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NEWS 1 Web Page URLs for STN Seminar Schedule - N. America
NEWS 2 "Ask CAS" for self-help around the clock
NEWS 3 FEB 28 PATDPAFULL - New display fields provide for legal status data from INPADOC
NEWS 4 FEB 28 BABS - Current-awareness alerts (SDIs) available
NEWS 5 MAR 02 GBFULL: New full-text patent database on STN
NEWS 6 MAR 03 REGISTRY/ZREGISTRY - Sequence annotations enhanced
NEWS 7 MAR 03 MEDLINE file segment of TOXCENTER reloaded
NEWS 8 MAR 22 KOREAPAT now updated monthly; patent information enhanced
NEWS 9 MAR 22 Original IDE display format returns to REGISTRY/ZREGISTRY
NEWS 10 MAR 22 PATDPASPC - New patent database available
NEWS 11 MAR 22 REGISTRY/ZREGISTRY enhanced with experimental property tags
NEWS 12 APR 04 EPFULL enhanced with additional patent information and new fields
NEWS 13 APR 04 EMBASE - Database reloaded and enhanced
NEWS 14 APR 18 New CAS Information Use Policies available online
NEWS 15 APR 25 Patent searching, including current-awareness alerts (SDIs), based on application date in CA/CAplus and USPATFULL/USPAT2 may be affected by a change in filing date for U.S. applications.
NEWS 16 APR 28 Improved searching of U.S. Patent Classifications for U.S. patent records in CA/CAplus
NEWS 17 MAY 23 GBFULL enhanced with patent drawing images
NEWS 18 MAY 23 REGISTRY has been enhanced with source information from CHEMCATS
NEWS 19 JUN 06 The Analysis Edition of STN Express with Discover! (Version 8.0 for Windows) now available
NEWS 20 JUN 13 RUSSIAPAT: New full-text patent database on STN
NEWS 21 JUN 13 FRFULL enhanced with patent drawing images
NEWS 22 JUN 27 MARPAT displays enhanced with expanded G-group definitions and text labels
NEWS 23 JUL 01 MEDICONF removed from STN
NEWS 24 JUL 07 STN Patent Forums to be held in July 2005
NEWS 25 JUL 13 SCISEARCH reloaded
NEWS 26 JUL 20 Powerful new interactive analysis and visualization software, STN AnaVist, now available

NEWS EXPRESS JUNE 13 CURRENT WINDOWS VERSION IS V8.0, CURRENT MACINTOSH VERSION IS V6.0c(ENG) AND V6.0Jc(JP), AND CURRENT DISCOVER FILE IS DATED 13 JUNE 2005

NEWS HOURS STN Operating Hours Plus Help Desk Availability
NEWS INTER General Internet Information
NEWS LOGIN Welcome Banner and News Items.
NEWS PHONE Direct Dial and Telecommunication Network Access to STN
NEWS WWW CAS World Wide Web Site (general information)

Enter NEWS followed by the item number or name to see news on that specific topic.

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*ENCOMPPAT - EnCompass Patent File 1964-present (Supporters)
*ENCOMPPAT2 - EnCompass Patent File 1964-Present (Non-Supporters)

* The files listed above are temporarily unavailable.

FILE 'HOME' ENTERED AT 13:01:12 ON 25 JUL 2005

FILE 'MEDLINE' ENTERED AT 13:01:25 ON 25 JUL 2005

FILE LAST UPDATED: 23 JUL 2005 (20050723/UP). FILE COVERS 1950 TO DATE.

On December 19, 2004, the 2005 MeSH terms were loaded.

The MEDLINE reload for 2005 is now available. For details enter HELP RLOAD at an arrow prompt (=>). See also:

<http://www.nlm.nih.gov/mesh/>
http://www.nlm.nih.gov/pubs/techbull/nd04/nd04_mesh.html

OLD MEDLINE now back to 1950.

MEDLINE thesauri in the /CN, /CT, and /MN fields incorporate the MeSH 2005 vocabulary.

This file contains CAS Registry Numbers for easy and accurate substance identification.

```
=> s WNT
      3897 WNT
      336 WNTS
L1    3942 WNT
          (WNT OR WNTS)
```

```
=> s 11 (S) antagon?  
      518406 ANTAGON?  
L2          244 L1 (S) ANTAGON?
```

=> s osteo? or bone
211167 OSTEOP?
424243 BONE
91740 BONES
446342 BONE
I.3 (BONE OR BONES)
553450 OSTEOP? OR BONE

=> s 13 and 12
T.4 70 T.3 AND T.2

=> s multiple myeloma
445180 MULTIPLE

3940 MULTIPLES
446855 MULTIPLE
 (MULTIPLE OR MULTIPLES)
30767 MYELOMA
763 MYELOMAS
31029 MYELOMA
 (MYELOMA OR MYELOMAS)
L5 22597 MULTIPLE MYELOMA
 (MULTIPLE (W) MYELOMA)

=> s 15 and 14
L6 1 L5 AND L4

=> d ibib 1

L6 ANSWER 1 OF 1 MEDLINE on STN
ACCESSION NUMBER: 2003612654 MEDLINE
DOCUMENT NUMBER: PubMed ID: 14695408
TITLE: The role of the Wnt-signaling antagonist
DKK1 in the development of osteolytic lesions in
multiple myeloma.
COMMENT: Comment in: N Engl J Med. 2003 Dec 25;349(26):2479-80.
 PubMed ID: 14695406
 Comment in: N Engl J Med. 2004 Apr 1;350(14):1464-6; author
 reply 1464-6. PubMed ID: 15070800
 Comment in: N Engl J Med. 2004 Apr 1;350(14):1464-6; author
 reply 1464-6. PubMed ID: 15074002
 Comment in: N Engl J Med. 2004 Apr 1;350(14):1464-6; author
 reply 1464-6. PubMed ID: 15074001
 Comment in: N Engl J Med. 2004 Jul 8;351(2):197-8. PubMed
 ID: 15247367
AUTHOR: Tian Ermeng; Zhan Fenghuang; Walker Ronald; Rasmussen Erik;
 Ma Yupo; Barlogie Bart; Shaughnessy John D Jr
CORPORATE SOURCE: Donna D. and Donald M. Lambert Laboratory of Myeloma
 Genetics, Myeloma Institute for Research and Therapy,
 College of Medicine, University of Arkansas for Medical
 Sciences, Little Rock 72205, USA.
CONTRACT NUMBER: CA97513 (NCI)
SOURCE: New England journal of medicine, (2003 Dec 25) 349 (26)
 2483-94.
PUB. COUNTRY: Journal code: 0255562. ISSN: 1533-4406.
DOCUMENT TYPE: United States
LANGUAGE: Journal; Article; (JOURNAL ARTICLE)
FILE SEGMENT: English
ENTRY MONTH: Abridged Index Medicus Journals; Priority Journals
200401
ENTRY DATE: Entered STN: 20031230
 Last Updated on STN: 20040107
 Entered Medline: 20040106

=> d his

(FILE 'HOME' ENTERED AT 13:01:12 ON 25 JUL 2005)

FILE 'MEDLINE' ENTERED AT 13:01:25 ON 25 JUL 2005
L1 3942 S WNT
L2 244 S L1 (S) ANTAGON?
L3 553450 S OSTEO? OR BONE
L4 70 S L3 AND L2
L5 22597 S MULTIPLE MYELOMA
L6 1 S L5 AND L4

=> s 12 and 15

L7 1 L2 AND L5

=> s myeloma
30767 MYELOMA
763 MYELOMAS
L8 31029 MYELOMA
(MYELOMA OR MYELOMAS)

=> s 18 and 12
L9 1 L8 AND L2

=> s 11 and 13
L10 451 L1 AND L3

=> s 110 and 15
L11 7 L10 AND L5

=> s 111 not py>2002
1489868 PY>2002
L12 1 L11 NOT PY>2002

=> d ibib

L12 ANSWER 1 OF 1 MEDLINE on STN
ACCESSION NUMBER: 2001420323 MEDLINE
DOCUMENT NUMBER: PubMed ID: 11468178
TITLE: Identifying intercellular signaling genes expressed in malignant plasma cells by using complementary DNA arrays.
AUTHOR: De Vos J; Couderc G; Tarte K; Jourdan M; Requirand G; Delteil M C; Rossi J F; Mechti N; Klein B
CORPORATE SOURCE: INSERM U475, Unit for Cellular Therapy, CHU Montpellier, 99 Rue Puech Villa, 34197 Montpellier Cedex 5, France.
SOURCE: Blood, (2001 Aug 1) 98 (3) 771-80.
Journal code: 7603509. ISSN: 0006-4971.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Abridged Index Medicus Journals; Priority Journals
ENTRY MONTH: 200109
ENTRY DATE: Entered STN: 20010917
Last Updated on STN: 20010917
Entered Medline: 20010913

=> d kwic

L12 ANSWER 1 OF 1 MEDLINE on STN
AB In multiple myeloma (MM), the growth of primary plasma cells depends not only on interleukin-6 (IL-6), but also on additional unidentified signals delivered by the bone marrow environment. Using Atlas complementary DNA (cDNA) arrays comprising 268 genes coding for intercellular signaling molecules, this study identified genes. . . receptor (TR) that is linked to HB-EGF and syndecan-1 processing and to cell invasion, chemokine receptors CCR1 and CCR2, the Wnt pathway actor Frizzled-related protein (FRZB), and the Notch receptor ligand Jagged 2. These data, obtained with the Atlas cDNA array,. . .
CT B-Lymphocytes: ME, metabolism
Cell Division: DE, drug effects
Epidermal Growth Factor: ME, metabolism
Flow Cytometry
Gene Expression: GE, genetics
Humans
Multiple Myeloma: GE, genetics
*Multiple Myeloma: ME, metabolism
Multiple Myeloma: PA, pathology

Neoplasm Proteins: GE, genetics
Neoplasm Proteins: ME, metabolism
*Oligonucleotide Array Sequence Analysis: MT, methods
*Plasma Cells: . . .

=> s (dickkopf () 1) or (DKK () 1)
85 DICKKOPF
8 DICKKOPFS
90 DICKKOPF
(DICKKOPF OR DICKKOPFS)
3513889 1
49 DICKKOPF (W) 1
119 DKK
9 DKKS
121 DKK
(DKK OR DKKS)
3513889 1
44 DKK (W) 1
L13 70 (DICKKOPF (W) 1) OR (DKK (W) 1)

=> d his

(FILE 'HOME' ENTERED AT 13:01:12 ON 25 JUL 2005)

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L2 244 S L1 (S) ANTAGON?
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L5 22597 S MULTIPLE MYELOMA
L6 1 S L5 AND L4
L7 1 S L2 AND L5
L8 31029 S MYELOMA
L9 1 S L8 AND L2
L10 451 S L1 AND L3
L11 7 S L10 AND L5
L12 1 S L11 NOT PY>2002
L13 70 S (DICKKOPF () 1) OR (DKK () 1)

=> s l13 and l11
L14 2 L13 AND L11

=> d ibib 1-2

L14 ANSWER 1 OF 2 MEDLINE on STN
ACCESSION NUMBER: 2005314981 IN-PROCESS
DOCUMENT NUMBER: PubMed ID: 15965110
TITLE: How wnt signaling affects bone repair
by mesenchymal stem cells from the bone marrow.
AUTHOR: Gregory Carl A; Gunn William G; Reyes Emigdio; Smolarz
Angela J; Munoz James; Spees Jeffrey L; Prockop Darwin J
CORPORATE SOURCE: Center for Gene Therapy, Tulane University Health Sciences
Center, 1430 Tulane Avenue, New Orleans, LA 70112..
ca_gregory@hotmail.com
SOURCE: Annals of the New York Academy of Sciences, (2005 May) 1049
97-106.
Journal code: 7506858. ISSN: 0077-8923.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: NONMEDLINE; IN-DATA-REVIEW; IN-PROCESS; NONINDEXED;
Priority Journals
ENTRY DATE: Entered STN: 20050621
Last Updated on STN: 20050621

L14 ANSWER 2 OF 2 MEDLINE on STN
ACCESSION NUMBER: 2003612654 MEDLINE
DOCUMENT NUMBER: PubMed ID: 14695408
TITLE: The role of the Wnt-signaling antagonist DKK1 in
the development of osteolytic lesions in
multiple myeloma.
COMMENT: Comment in: N Engl J Med. 2003 Dec 25;349(26):2479-80.
PubMed ID: 14695406
Comment in: N Engl J Med. 2004 Apr 1;350(14):1464-6; author
reply 1464-6. PubMed ID: 15070800
Comment in: N Engl J Med. 2004 Apr 1;350(14):1464-6; author
reply 1464-6. PubMed ID: 15074002
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Comment in: N Engl J Med. 2004 Jul 8;351(2):197-8. PubMed
ID: 15247367
AUTHOR: Tian Ermeng; Zhan Fenghuang; Walker Ronald; Rasmussen Erik;
Ma Yupo; Barlogie Bart; Shaughnessy John D Jr
CORPORATE SOURCE: Donna D. and Donald M. Lambert Laboratory of Myeloma
Genetics, Myeloma Institute for Research and Therapy,
College of Medicine, University of Arkansas for Medical
Sciences, Little Rock 72205, USA.
CONTRACT NUMBER:
CA97513 (NCI)
SOURCE: New England journal of medicine, (2003 Dec 25) 349 (26)
2483-94.
PUB. COUNTRY: Journal code: 0255562. ISSN: 1533-4406.
DOCUMENT TYPE: United States
LANGUAGE: Journal; Article; (JOURNAL ARTICLE)
FILE SEGMENT: English
ENTRY MONTH: Abridged Index Medicus Journals; Priority Journals
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ENTRY DATE: Entered STN: 20031230
Last Updated on STN: 20040107
Entered Medline: 20040106

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L9 1 S L8 AND L2
L10 451 S L1 AND L3
L11 7 S L10 AND L5
L12 1 S L11 NOT PY>2002
L13 70 S (DICKKOPF () 1) OR (DKK () 1)
L14 2 S L13 AND L11

=> d ibib kwic 112

L12 ANSWER 1 OF 1 MEDLINE on STN
ACCESSION NUMBER: 2001420323 MEDLINE
DOCUMENT NUMBER: PubMed ID: 11468178
TITLE: Identifying intercellular signaling genes expressed in
malignant plasma cells by using complementary DNA arrays.

AUTHOR: De Vos J; Couderc G; Tarte K; Jourdan M; Requirand G;
Delteil M C; Rossi J F; Mechti N; Klein B
CORPORATE SOURCE: INSERM U475, Unit for Cellular Therapy, CHU Montpellier, 99
Rue Puech Villa, 34197 Montpellier Cedex 5, France.
SOURCE: Blood, (2001 Aug 1) 98 (3) 771-80.
Journal code: 7603509. ISSN: 0006-4971.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Abridged Index Medicus Journals; Priority Journals
ENTRY MONTH: 200109
ENTRY DATE: Entered STN: 20010917
Last Updated on STN: 20010917
Entered Medline: 20010913
AB In multiple myeloma (MM), the growth of primary plasma
cells depends not only on interleukin-6 (IL-6), but also on additional
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Using Atlas complementary DNA (cDNA) arrays comprising 268 genes coding
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receptor (TR) that is linked to HB-EGF and syndecan-1 processing and to
cell invasion, chemokine receptors CCR1 and CCR2, the Wnt
pathway actor Frizzled-related protein (FRZB), and the Notch receptor
ligand Jagged 2. These data, obtained with the Atlas cDNA array,
CT B-Lymphocytes: ME, metabolism
Cell Division: DE, drug effects
Epidermal Growth Factor: ME, metabolism
Flow Cytometry
Gene Expression: GE, genetics
Humans
Multiple Myeloma: GE, genetics
*Multiple Myeloma: ME, metabolism
Multiple Myeloma: PA, pathology
Neoplasm Proteins: GE, genetics
Neoplasm Proteins: ME, metabolism
*Oligonucleotide Array Sequence Analysis: MT, methods
*Plasma Cells: . . .

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(FILE 'HOME' ENTERED AT 13:01:12 ON 25 JUL 2005)

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L1 3942 S WNT
L2 244 S L1 (S) ANTAGON?
L3 553450 S OSTEO? OR BONE
L4 70 S L3 AND L2
L5 22597 S MULTIPLE MYELOMA
L6 1 S L5 AND L4
L7 1 S L2 AND L5
L8 31029 S MYELOMA
L9 1 S L8 AND L2
L10 451 S L1 AND L3
L11 7 S L10 AND L5
L12 1 S L11 NOT PY>2002
L13 70 S (DICKKOPF () 1) OR (DKK () 1)
L14 2 S L13 AND L11

=> s l13 and 13.

L15 19 L13 AND L3

=> s l15 and express?

932565 EXPRESS?

L16 14 L15 AND EXPRESS?

=> s l16 not py>2002
1489868 PY>2002
L17 6 L16 NOT PY>2002

=> d ibib 1-3

L17 ANSWER 1 OF 6 MEDLINE on STN
ACCESSION NUMBER: 2002693855 MEDLINE
DOCUMENT NUMBER: PubMed ID: 12455632
TITLE: Bmp, Fgf and Wnt signalling in programmed cell death and chondrogenesis during vertebrate limb development: the role of Dickkopf-1.
AUTHOR: Grotewold Lars; Ruther Ulrich
CORPORATE SOURCE: Institut fur Entwicklungs- und Molekularbiologie der Tiere (EMT), Heinrich-Heine-Universitat, Dusseldorf, Germany.
SOURCE: International journal of developmental biology, (2002) 46 (7) 943-7.
Journal code: 8917470. ISSN: 0214-6282.
PUB. COUNTRY: Spain
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200306
ENTRY DATE: Entered STN: 20021214
Last Updated on STN: 20030619
Entered Medline: 20030618

L17 ANSWER 2 OF 6 MEDLINE on STN
ACCESSION NUMBER: 2002280313 MEDLINE
DOCUMENT NUMBER: PubMed ID: 12021176
TITLE: Global gene profiling in human endometrium during the window of implantation.
AUTHOR: Kao L C; Tulac S; Lobo S; Imani B; Yang J P; Germeyer A; Osteen K; Taylor R N; Lessey B A; Giudice L C
CORPORATE SOURCE: Department of Gynecology and Obstetrics, Stanford University, Stanford, California 94305, USA.
CONTRACT NUMBER: U54 HD31398 (NICHD)
SOURCE: Endocrinology, (2002 Jun) 143 (6) 2119-38.
Journal code: 0375040. ISSN: 0013-7227.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Abridged Index Medicus Journals; Priority Journals
ENTRY MONTH: 200206
ENTRY DATE: Entered STN: 20020522
Last Updated on STN: 20020619
Entered Medline: 20020618

L17 ANSWER 3 OF 6 MEDLINE on STN
ACCESSION NUMBER: 2002131765 MEDLINE
DOCUMENT NUMBER: PubMed ID: 11867524
TITLE: The Wnt antagonist Dickkopf-1 is regulated by Bmp signaling and c-Jun and modulates programmed cell death.
AUTHOR: Grotewold Lars; Ruther Ulrich
CORPORATE SOURCE: Entwicklungs- und Molekularbiologie der Tiere, Heinrich-Heine Universitat, D-40225 Dusseldorf, Germany..
lars.grotewold@uni-duesseldorf.de
SOURCE: EMBO journal, (2002 Mar 1) 21 (5) 966-75.
Journal code: 8208664. ISSN: 0261-4189.
PUB. COUNTRY: England: United Kingdom
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200205

ENTRY DATE: Entered STN: 20020228
Last Updated on STN: 20020515
Entered Medline: 20020514

=> d ibib 4-6

L17 ANSWER 4 OF 6 MEDLINE on STN
ACCESSION NUMBER: 2001447406 MEDLINE
DOCUMENT NUMBER: PubMed ID: 11291860
TITLE: The role of the homeodomain protein Bozozok in zebrafish axis formation.
AUTHOR: Solnica-Krezel L; Driever W
CORPORATE SOURCE: Department of Molecular Biology, Vanderbilt University, Nashville, Tennessee 37235, USA.. lilianna.solnica-krezel@vanderbilt.edu
SOURCE: International journal of developmental biology, (2001) 45 (1) 299-310.
Journal code: 8917470. ISSN: 0214-6282.
PUB. COUNTRY: Spain
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200108
ENTRY DATE: Entered STN: 20010813
Last Updated on STN: 20010813
Entered Medline: 20010809

L17 ANSWER 5 OF 6 MEDLINE on STN
ACCESSION NUMBER: 2001150174 MEDLINE
DOCUMENT NUMBER: PubMed ID: 11159911
TITLE: Wnt antagonism initiates cardiogenesis in *Xenopus laevis*.
AUTHOR: Schneider V A; Mercola M
CORPORATE SOURCE: Department of Cell Biology, Harvard Medical School, Boston, Massachusetts 02115, USA.
CONTRACT NUMBER: R01 HL59502 (NHLBI)
SOURCE: Genes & development, (2001 Feb 1) 15 (3) 304-15.
Journal code: 8711660. ISSN: 0890-9369.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200103
ENTRY DATE: Entered STN: 20010404
Last Updated on STN: 20010404
Entered Medline: 20010315

L17 ANSWER 6 OF 6 MEDLINE on STN
ACCESSION NUMBER: 1999425169 MEDLINE
DOCUMENT NUMBER: PubMed ID: 10495270
TITLE: Dickkopf genes are co-ordinately expressed in mesodermal lineages.
AUTHOR: Monaghan A P; Kioschis P; Wu W; Zuniga A; Bock D; Poustka A; Delius H; Niehrs C
CORPORATE SOURCE: Division of Molecular Biology of the Cell I, Deutsches Krebsforschungszentrum, Im Neuenheimer Feld 280, D-69120, Heidelberg, Germany.
SOURCE: Mechanisms of development, (1999 Sep) 87 (1-2) 45-56.
Journal code: 9101218. ISSN: 0925-4773.
PUB. COUNTRY: Ireland
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
OTHER SOURCE: GENBANK-AJ243963; GENBANK-AJ243964
ENTRY MONTH: 200003

ENTRY DATE: Entered STN: 20000327
Last Updated on STN: 20000327
Entered Medline: 20000316

=> d kwic 6

L17 ANSWER 6 OF 6 MEDLINE on STN
TI Dickkopf genes are co-ordinately expressed in mesodermal lineages.
AB Dickkopf-1 (dkk-1) is member of a novel family of secreted proteins and functions in head induction during Xenopus embryogenesis, acting as a . . . of two additional murine members of the dkk family, dkk-2 and dkk-3; and (2) analysis of adult and embryonic gene expression of mouse dkk-1,-2, and -3, Xenopus dkk-1 as well as chicken dkk-3. Comparative developmental analyses of the dkk-1, dkk-2 and dkk-3 in mice indicate that these genes are both temporally and spatially regulated. They define overlapping deep domains in mesenchymal lineages suggesting a co-ordinated mode of action. All dkks show distinct and elevated expression patterns in tissues that mediate epithelial- mesenchyme transformations suggesting that they may participate in heart, tooth, hair and whisker follicle, limb and bone induction. In the limb buds expression of these genes are found in regions of programmed cell death. In a given organ, dkk-1 tends to be the earliest member expressed . Comparison with Xenopus dkk-1 and chicken dkk-3 shows evolutionarily conserved expression patterns. Our observations indicate that dkk genes constitute a new family of secreted proteins that may mediate inductive interactions between. . .

CT Amino Acid Sequence
Animals
Entrez Gene ME

CT Amino Acid Sequence
Animals
Ectoderm: ME, metabolism
Epithelial Cells: ME, me
*Gene Expression Regula
In Situ Hybridization
*Mesoderm: ME, metabolism
Mice
Molecular Sequence Data
*Proteins: GE, genetics
*Proteins: ME, metabolism
Reverse.

=> file caplus
COST IN U.S. DOLLARS

SINCE FILE ENTRY	TOTAL SESSION
5.44	5.65

FILE 'CAPLUS' ENTERED AT 13:06:53 ON 25 JUL 2005
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FILE COVERS 1907 - 25 Jul 2005 VOL 143 ISS 5
FILE LAST UPDATED: 24 Jul 2005 (20050724/ED)

New CAS Information Use Policies, enter HELP USAGETERMS for details.

This file contains CAS Registry Numbers for easy and accurate substance identification.

=> s WNT
4331 WNT
330 WNTS
L18 4365 WNT
(WNT OR WNTS)

=> s 11 (S) antagonist?
4331 WNT
330 WNTS
4365 WNT
(WNT OR WNTS)
270850 ANTAGON?
L19 273 L1 (S) ANTAGON?

=> s 118 (S) antagonist?
270850 ANTAGON?
L20 273 L18 (S) ANTAGON?

=> s myeloma
16718 MYELOMA
557 MYELOMAS
L21 16913 MYELOMA
(MYELOMA OR MYELOMAS)

=> s 120 and 121
L22 5 L20 AND L21

=> d ibib 1-3

L22 ANSWER 1 OF 5 CAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 2005:450819 CAPLUS
DOCUMENT NUMBER: 142:461611
TITLE: Diagnosis, prognosis and identification of potential therapeutic targets of multiple myeloma based on gene expression profiling
INVENTOR(S): Shaughnessy, John D.; Barlogie, Bart; Zhan, Fenghuang
PATENT ASSIGNEE(S): USA
SOURCE: U.S. Pat. Appl. Publ., 80 pp., Cont.-in-part of U.S. Ser. No. 454,263.
CODEN: USXXCO
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 4
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
US 2005112630	A1	20050526	US 2004-931780	20040901
US 2003175753	A1	20030918	US 2002-289746	20021107
US 2003232364	A1	20031218	US 2003-409004	20030408
US 2004009523	A1	20040115	US 2003-454263	20030604
PRIORITY APPLN. INFO.:			US 2001-348238P	P 20011107
			US 2002-355386P	P 20020208
			US 2002-403075P	P 20020813
			US 2002-289746	A2 20021107
			US 2003-409004	A2 20030408
			US 2003-454263	A2 20030604

L22 ANSWER 2 OF 5 CAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 2004:992468 CAPLUS
DOCUMENT NUMBER: 142:371352
TITLE: Wnt signaling antagonist DKK1 in
the development of osteolytic lesion in multiple
myeloma
AUTHOR(S): Sato, Kanji
CORPORATE SOURCE: Institute of Clinical Endocrinology, Tokyo
Women's Medical University, Tokyo, 162-8666,
Japan
SOURCE: Ketsueki, Shuyoka (2004), 49(2), 166-170
CODEN: KETSBI; ISSN: 0915-8529
PUBLISHER: Kagaku Hyoronsha
DOCUMENT TYPE: Journal; General Review
LANGUAGE: Japanese

L22 ANSWER 3 OF 5 CAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 2004:515641 CAPLUS
DOCUMENT NUMBER: 141:52350
TITLE: Expression of genes DKK1 and FRZB as molecular
determinants of myeloma bone disease and
transcription regulation for treatment thereof
INVENTOR(S): Shaughnessy, John D.
PATENT ASSIGNEE(S): The Board of Trustees of the University of Arkansas,
USA
SOURCE: PCT Int. Appl., 89 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2004053063	A2	20040624	WO 2003-US38372	20031204
WO 2004053063	A3	20041125		
W: AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SK, SL, TJ, TM, TR, TT, UA, UG, UZ, VN, YU, ZA, ZW RW: BW, GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PT, RO, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG				
US 2004137489	A1	20040715	US 2003-727461	20031204
PRIORITY APPLN. INFO.:			US 2002-431040P	P 20021205

=> d ibib 4-5

L22 ANSWER 4 OF 5 CAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 2004:40999 CAPLUS
DOCUMENT NUMBER: 140:109553
TITLE: Diagnosis, prognosis and identification of potential
therapeutic targets of multiple myeloma
based on gene expression profiling
INVENTOR(S): Shaughnessy, John D.; Zhan, Fenghuang; Barlogie, Bart
PATENT ASSIGNEE(S): USA
SOURCE: U.S. Pat. Appl. Publ., 67 pp., Cont.-in-part of U.S.
Ser. No. 409,004.
CODEN: USXXCO
DOCUMENT TYPE: Patent
LANGUAGE: English

FAMILY ACC. NUM. COUNT: 4

PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
US 2004009523	A1	20040115	US 2003-454263	20030604
US 2003175753	A1	20030918	US 2002-289746	20021107
US 2003232364	A1	20031218	US 2003-409004	20030408
US 2005112630	A1	20050526	US 2004-931780	20040901
PRIORITY APPLN. INFO.:				
			US 2001-348238P	P 20011107
			US 2002-355386P	P 20020208
			US 2002-403075P	P 20020813
			US 2002-289746	A2 20021107
			US 2003-409004	A2 20030408
			US 2003-454263	A2 20030604

L22 ANSWER 5 OF 5 CAPLUS COPYRIGHT 2005 ACS on STN

ACCESSION NUMBER: 2003:1011522 CAPLUS

DOCUMENT NUMBER: 140:126264

TITLE: The role of the Wnt-signaling antagonist DKK1 in the development of osteolytic lesions in multiple myeloma

AUTHOR(S): Tian, Ermeng; Zhan, Fenghuang; Walker, Ronald; Rasmussen, Erik; Ma, Yupo; Barlogie, Bart; Shaughnessy, John D., Jr.

CORPORATE SOURCE: Donna D. and Donald M. Lambert Laboratory of Myeloma Genetics, Myeloma Institute for Research and Therapy, College of Medicine, University of Arkansas for Medical Sciences, Little Rock, AR, USA

SOURCE: New England Journal of Medicine (2003), 349(26), 2483-2494

CODEN: NEJMAG; ISSN: 0028-4793

PUBLISHER: Massachusetts Medical Society

DOCUMENT TYPE: Journal

LANGUAGE: English

REFERENCE COUNT: 41 THERE ARE 41 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

=> s (dickkopf (), 1) or (DKK () 1)
175 DICKKOPF
8 DICKKOPFS
177 DICKKOPF
(DICKKOPF OR DICKKOPFS)

8339167 1
104 DICKKOPF (W) 1
123 DKK
11 DKKS
124 DKK
(DKK OR DKKS)

8339167 1
58 DKK (W) 1

L23 123 (DICKKOPF (W) 1) OR (DKK (W) 1)

=> s dickkopf-1 or DKK1
175 DICKKOPF
8 DICKKOPFS
177 DICKKOPF
(DICKKOPF OR DICKKOPFS)

8339167 1
104 DICKKOPF-1
(DICKKOPF(W)1)
98 DKK1

L24 155 DICKKOPF-1 OR DKK1

=> s 123 or 124
L25 170 L23 OR L24

=> s osteo?
L26 61795 OSTEO?

=> s 126 and 125
L27 32 L26 AND L25

=> d his

(FILE 'HOME' ENTERED AT 13:01:12 ON 25 JUL 2005)

FILE 'MEDLINE' ENTERED AT 13:01:25 ON 25 JUL 2005

L1 3942 S WNT
L2 244 S L1 (S) ANTAGON?
L3 553450 S OSTEO? OR BONE
L4 70 S L3 AND L2
L5 22597 S MULTIPLE MYELOMA
L6 1 S L5 AND L4
L7 1 S L2 AND L5
L8 31029 S MYELOMA
L9 1 S L8 AND L2
L10 451 S L1 AND L3
L11 7 S L10 AND L5
L12 1 S L11 NOT PY>2002
L13 70 S (DICKKOPF () 1) OR (DKK () 1)
L14 2 S L13 AND L11
L15 19 S L13 AND L3
L16 14 S L15 AND EXPRESS?
L17 6 S L16 NOT PY>2002

FILE 'CAPLUS' ENTERED AT 13:06:53 ON 25 JUL 2005

L18 4365 S WNT
L19 273 S L1 (S) ANTAGON?
L20 273 S L18 (S) ANTAGON?
L21 16913 S MYELOMA
L22 5 S L20 AND L21
L23 123 S (DICKKOPF () 1) OR (DKK () 1)
L24 155 S DICKKOPF-1 OR DKK1
L25 170 S L23 OR L24
L26 61795 S OSTEO?
L27 32 S L26 AND L25

=> s 127 and 121
L28 7 L27 AND L21

=> d ibib 1-4

L28 ANSWER 1 OF 7 CAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 2005:450819 CAPLUS
DOCUMENT NUMBER: 142:461611
TITLE: Diagnosis, prognosis and identification of potential therapeutic targets of multiple myeloma based on gene expression profiling
INVENTOR(S): Shaughnessy, John D.; Barlogie, Bart; Zhan, Fenghuang
PATENT ASSIGNEE(S): USA
SOURCE: U.S. Pat. Appl. Publ., 80 pp., Cont.-in-part of U.S. Ser. No. 454,263.
CODEN: USXXCO
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 4
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
US 2005112630	A1	20050526	US 2004-931780	20040901
US 2003175753	A1	20030918	US 2002-289746	20021107
US 2003232364	A1	20031218	US 2003-409004	20030408
US 2004009523	A1	20040115	US 2003-454263	20030604
PRIORITY APPLN. INFO.:				
			US 2001-348238P	P 20011107
			US 2002-355386P	P 20020208
			US 2002-403075P	P 20020813
			US 2002-289746	A2 20021107
			US 2003-409004	A2 20030408
			US 2003-454263	A2 20030604

L28 ANSWER 2 OF 7 CAPLUS COPYRIGHT 2005 ACS on STN
 ACCESSION NUMBER: 2005:348815 CAPLUS
 DOCUMENT NUMBER: 142:397651
 TITLE: Inhibitors of protein Dickkopf-1
 for treating osteolytic lesions in multiple
 myeloma and enhancing osteogenesis
 INVENTOR(S): Prockop, Darwin; Gregory, Carl; Gunn, William
 PATENT ASSIGNEE(S): USA
 SOURCE: U.S. Pat. Appl. Publ., 84 pp., Cont.-in-part of U.S.
 Ser. No. 830,352, abandoned.
 CODEN: USXXCO
 DOCUMENT TYPE: Patent
 LANGUAGE: English
 FAMILY ACC. NUM. COUNT: 2
 PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
US 2005084494	A1	20050421	US 2004-839515	20040505
US 2004235166	A1	20041125	US 2003-442506	20030521
PRIORITY APPLN. INFO.:				
			US 2003-442506	A2 20030521
			US 2004-830352	B2 20040422

L28 ANSWER 3 OF 7 CAPLUS COPYRIGHT 2005 ACS on STN
 ACCESSION NUMBER: 2004:992468 CAPLUS
 DOCUMENT NUMBER: 142:371352
 TITLE: Wnt signaling antagonist DKK1 in the
 development of osteolytic lesion in multiple
 myeloma
 AUTHOR(S): Sato, Kanji
 CORPORATE SOURCE: Institute of Clinical Endocrinology, Tokyo
 Women's Medical University, Tokyo, 162-8666,
 Japan
 SOURCE: Ketsueki, Shuyoka (2004), 49(2), 166-170
 CODEN: KETSBI; ISSN: 0915-8529
 PUBLISHER: Kagaku Hyoronsha
 DOCUMENT TYPE: Journal; General Review
 LANGUAGE: Japanese

L28 ANSWER 4 OF 7 CAPLUS COPYRIGHT 2005 ACS on STN
 ACCESSION NUMBER: 2004:515641 CAPLUS
 DOCUMENT NUMBER: 141:52350
 TITLE: Expression of genes DKK1 and FRZB as
 molecular determinants of myeloma bone
 disease and transcription regulation for treatment
 thereof
 INVENTOR(S): Shaughnessy, John D.
 PATENT ASSIGNEE(S): The Board of Trustees of the University of Arkansas,
 USA
 SOURCE: PCT Int. Appl., 89 pp.
 CODEN: PIXXD2
 DOCUMENT TYPE: Patent

LANGUAGE: English

FAMILY ACC. NUM. COUNT: 1

PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2004053063	A2	20040624	WO 2003-US38372	20031204
WO 2004053063	A3	20041125		
W:	AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SK, SL, TJ, TM, TR, TT, UA, UG, UZ, VN, YU, ZA, ZW			
RW:	BW, GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PT, RO, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG			
US 2004137489	A1	20040715	US 2003-727461	20031204
PRIORITY APPLN. INFO.:			US 2002-431040P	P 20021205

=> d ibib 5-7

L28 ANSWER 5 OF 7 CAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 2004:504577 CAPLUS
DOCUMENT NUMBER: 141:219048
TITLE: Activation mechanism of osteoclasts
AUTHOR(S): Sato, Kanji
CORPORATE SOURCE: Dep. of Medicine II, Tokyo Women's Medical University, Tokyo, 162-8666, Japan
SOURCE: Ketsueki, Shuyoka (2004), 48(3), 274-280
CODEN: KETSBI; ISSN: 0915-8529
PUBLISHER: Kagaku Hyoronsha
DOCUMENT TYPE: Journal; General Review
LANGUAGE: Japanese

L28 ANSWER 6 OF 7 CAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 2004:40999 CAPLUS
DOCUMENT NUMBER: 140:109553
TITLE: Diagnosis, prognosis and identification of potential therapeutic targets of multiple myeloma based on gene expression profiling
INVENTOR(S): Shaughnessy, John D.; Zhan, Fenghuang; Barlogie, Bart USA
PATENT ASSIGNEE(S):
SOURCE: U.S. Pat. Appl. Publ., 67 pp., Cont.-in-part of U.S. Ser. No. 409,004.
CODEN: USXXCO
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 4
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
US 2004009523	A1	20040115	US 2003-454263	20030604
US 2003175753	A1	20030918	US 2002-289746	20021107
US 2003232364	A1	20031218	US 2003-409004	20030408
US 2005112630	A1	20050526	US 2004-931780	20040901
PRIORITY APPLN. INFO.:			US 2001-348238P	P 20011107
			US 2002-355386P	P 20020208
			US 2002-403075P	P 20020813
			US 2002-289746	A2 20021107
			US 2003-409004	A2 20030408
			US 2003-454263	A2 20030604

L28 ANSWER 7 OF 7 CAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 2003:1011522 CAPLUS
DOCUMENT NUMBER: 140:126264
TITLE: The role of the Wnt-signaling antagonist DKK1
in the development of osteolytic lesions in
multiple myeloma
AUTHOR(S): Tian, Ermjing; Zhan, Fenghuang; Walker, Ronald;
Rasmussen, Erik; Ma, Yupo; Barlogie, Bart;
Shaughnessy, John D., Jr.
CORPORATE SOURCE: Donna D. and Donald M. Lambert Laboratory of Myeloma
Genetics, Myeloma Institute for Research and Therapy,
College of Medicine, University of Arkansas for
Medical Sciences, Little Rock, AR, USA
SOURCE: New England Journal of Medicine (2003), 349(26),
2483-2494
PUBLISHER: Massachusetts Medical Society
DOCUMENT TYPE: Journal
LANGUAGE: English
REFERENCE COUNT: 41 THERE ARE 41 CITED REFERENCES AVAILABLE FOR THIS
RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

=> file pctfull
COST IN U.S. DOLLARS
FULL ESTIMATED COST SINCE FILE TOTAL
ENTRY SESSION
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FILE 'PCTFULL' ENTERED AT 13:10:21 ON 25 JUL 2005
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FILE LAST UPDATED: 19 JUL 2005 <20050719/UP>
MOST RECENT UPDATE WEEK: 200528 <200528/EW>
FILE COVERS 1978 TO DATE

>>> IMAGES ARE AVAILABLE ONLINE AND FOR EMAIL-PRINTS <<<

=> s WNT
1265 WNT
148 WNTS
L29 1307 WNT
(WNT OR WNTS)

=> s l29 (s) antag?
48582 ANTAG?
L30 161 L29 (S) ANTAG?

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106 DICKKOPF
4 DICKKOPFS
107 DICKKOPF
(DICKKOPF OR DICKKOPFS)

920163 1
20 DICKKOPF (W) 1
178 DKK
16 DKKS
181 DKK
(DKK OR DKKS)

920163 1
40 DKK (W) 1
L31 46 (DICKKOPF (W) 1) OR (DKK (W) 1)

=> s dickkopf-1 or DKK1 or DKK-1
106 DICKKOPF
4 DICKKOPFS

107 DICKKOPF
(DICKKOPF OR DICKKOPFS)
920163 1
20 DICKKOPF-1
(DICKKOPF(W) 1)
26 DKK1
178 DKK
16 DKKS
181 DKK
(DKK OR DKKS)
920163 1
40 DKK-1
(DKK(W) 1)
L32 62 DICKKOPF-1 OR DKK1 OR DKK-1

=> s 132 or 131
L33 62 L32 OR L31

=> s osteo?
L34 27031 OSTEO?

=> s 134 or bone
48366 BONE
8795 BONES
50481 BONE
(BONE OR. BONES)
L35 59451 L34 OR BONE

=> s cancer? or tumor? or neoplas?
70033 CANCER?
58772 TUMOR?
20120 NEOPLAS?
L36 87552 CANCER? OR TUMOR? OR NEOPLAS?

=> s myeloma
14084 MYELOMA
1344 MYELOMAS
L37 14570 MYELOMA
(MYELOMA OR MYELOMAS)

=> d his

(FILE 'HOME' ENTERED AT 13:01:12 ON 25 JUL 2005)

FILE 'MEDLINE' ENTERED AT 13:01:25 ON 25 JUL 2005
L1 3942 S WNT
L2 244 S L1 (S) ANTAGON?
L3 553450 S OSTEO? OR BONE
L4 70 S L3 AND L2
L5 22597 S MULTIPLE MYELOMA
L6 1 S L5 AND L4
L7 1 S L2 AND L5
L8 31029 S MYELOMA
L9 1 S L8 AND L2
L10 451 S L1 AND L3
L11 7 S L10 AND L5
L12 1 S L11 NOT PY>2002
L13 70 S (DICKKOPF () 1) OR (DKK () 1)
L14 2 S L13 AND L11
L15 19 S L13 AND L3
L16 14 S L15 AND EXPRESS?
L17 6 S L16 NOT PY>2002

FILE 'CAPLUS' ENTERED AT 13:06:53 ON 25 JUL 2005
L18 4365 S WNT

L19 273 S L1 (S) ANTAGON?
L20 273 S L18 (S) ANTAGON?
L21 16913 S MYELOMA
L22 5 S L20 AND L21
L23 123 S (DICKKOPF () 1) OR (DKK () 1)
L24 155 S DICKKOPF-1 OR DKK1
L25 170 S L23 OR L24
L26 61795 S OSTEO?
L27 32 S L26 AND L25
L28 7 S L27 AND L21

FILE 'PCTFULL' ENTERED AT 13:10:21 ON 25 JUL 2005

L29 1307 S WNT
L30 161 S L29 (S) ANTAG?
L31 46 S (DICKKOPF () 1) OR (DKK () 1)
L32 62 S DICKKOPF-1 OR DKK1 OR DKK-1
L33 62 S L32 OR L31
L34 27031 S OSTEO?
L35 59451 S L34 OR BONE
L36 87552 S CANCER? OR TUMOR? OR NEOPLAS?
L37 14570 S MYELOMA

=> s 162 and 135

L62 NOT FOUND.

The L-number entered could not be found. To see the definition of L-numbers, enter DISPLAY HISTORY at an arrow prompt (>).

=> s 133 and 134
L38 39 L33 AND L34

=> s 138 and 137
L39 18 L38 AND L37

=> s 139 not py>2002
287458 PY>2002
L40 8 L39 NOT PY>2002

=> s 133/clm
16 DICKKOPF/CLM
870322 1/CLM
3 DICKKOPF-1/CLM
((DICKKOPF(W)1)/CLM)
5 DKK1/CLM
26 DKK/CLM
870322 1/CLM
5 DKK-1/CLM
((DKK(W)1)/CLM)
16 DICKKOPF/CLM
870322 1/CLM
3 DICKKOPF/CLM (W) 1/CLM
26 DKK/CLM
870322 1/CLM
5 DKK/CLM (W) 1/CLM
L41 10 ((DICKKOPF-1/CLM OR DKK1/CLM OR DKK-1/CLM) OR ((DICKKOPF/CLM (W) 1/CLM) OR (DKK/CLM (W) 1/CLM)))

=> s 141 and 140
L42 1 L41 AND L40

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L42 ANSWER 1 OF 1 PCTFULL COPYRIGHT 2005 Univentio on STN
ACCESSION NUMBER: 2002066509 PCTFULL ED 20020910 EW 200235
TITLE (ENGLISH): TREATMENT INVOLVING DKK-1 OR
ANTAGONISTS THEREOF

TITLE (FRENCH): TRAITEMENT FAISANT APPEL A DKK-1 OU
 AUX ANTAGONISTES DE DKK-1
 INVENTOR(S): DeALMEIDA, Venita I., 3014 Los Prados Avenue, #A116,
 San Mateo, CA 94403, US;
 STEWART, Timothy A., 465 Douglas Street, San Francisco,
 CA 94114, US
 PATENT ASSIGNEE(S): GENENTECH, INC., 1 DNA Way, South San Francisco, CA
 94080, US [US, US]
 AGENT: HASAK, Janet E.S., GENENTECH, INC., MS 49, 1 DNA Way,
 South San Francisco, CA 94080-4990\$, US
 LANGUAGE OF FILING: English
 LANGUAGE OF PUBL.: English
 DOCUMENT TYPE: Patent
 PATENT INFORMATION:

NUMBER	KIND	DATE
WO 2002066509	A2	20020829

 DESIGNATED STATES
 W: AE AG AL AM AT AU AZ BA BB BG BR BY BZ CA CH CN CO CR
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 IL IN IS JP KE KG KP KR KZ LC LK LR LS LT LU LV MA MD
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 SK SL TJ TM TN TR TT TZ UA UG UZ VN YU ZA ZM ZW
 RW (ARIPO): GH GM KE LS MW MZ SD SL SZ TZ UG ZM ZW
 RW (EAPO): AM AZ BY KG KZ MD RU TJ TM
 RW (EPO): AT BE CH CY DE DK ES FI FR GB GR IE IT LU MC NL PT SE
 TR
 RW (OAPI): BF BJ CF CG CI CM GA GN GQ GW ML MR NE SN TD TG
 APPLICATION INFO.: WO 2002-US4573 A 20020215
 PRIORITY INFO.: US 2001-60/269,435 20010216

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(FILE 'HOME' ENTERED AT 13:01:12 ON 25 JUL 2005)

FILE 'MEDLINE' ENTERED AT 13:01:25 ON 25 JUL 2005
 L1 3942 S WNT
 L2 244 S L1 (S) ANTAGON?
 L3 553450 S OSTEO? OR BONE
 L4 70 S L3 AND L2
 L5 22597 S MULTIPLE MYELOMA
 L6 1 S L5 AND L4
 L7 1 S L2 AND L5
 L8 31029 S MYELOMA
 L9 1 S L8 AND L2
 L10 451 S L1 AND L3
 L11 7 S L10 AND L5
 L12 1 S L11 NOT PY>2002
 L13 70 S (DICKKOPF () 1) OR (DKK () 1)
 L14 2 S L13 AND L11
 L15 19 S L13 AND L3
 L16 14 S L15 AND EXPRESS?
 L17 6 S L16 NOT PY>2002

FILE 'CAPLUS' ENTERED AT 13:06:53 ON 25 JUL 2005
 L18 4365 S WNT
 L19 273 S L1 (S) ANTAGON?
 L20 273 S L18 (S) ANTAGON?
 L21 16913 S MYELOMA
 L22 5 S L20 AND L21
 L23 123 S (DICKKOPF () 1) OR (DKK () 1)
 L24 155 S DICKKOPF-1 OR DKK1
 L25 170 S L23 OR L24
 L26 61795 S OSTEO?

L27 32 S L26 AND L25
L28 7 S L27 AND L21

FILE 'PCTFULL' ENTERED AT 13:10:21 ON 25 JUL 2005

L29 1307 S WNT
L30 161 S L29 (S) ANTAG?
L31 46 S (DICKKOPF () 1) OR (DKK () 1)
L32 62 S DICKKOPF-1 OR DKK1 OR DKK-1
L33 62 S L32 OR L31
L34 27031 S OSTEO?
L35 59451 S L34 OR BONE
L36 87552 S CANCER? OR TUMOR? OR NEOPLAS?
L37 14570 S MYELOMA
L38 39 S L33 AND L34
L39 18 S L38 AND L37
L40 8 S L39 NOT PY>2002
L41 10 S L33/CLM
L42 1 S L41 AND L40

=> s l33/ab

5 DICKKOPF/AB
221598 1/AB
3 DICKKOPF-1/AB
 ((DICKKOPF(W) 1)/AB)
1 DKK1/AB
5 DKK/AB
221598 1/AB
2 DKK-1/AB
 ((DKK(W) 1)/AB)
5 DICKKOPF/AB
221598 1/AB
3 DICKKOPF/AB (W) 1/AB
5 DKK/AB
221598 1/AB
2 DKK/AB (W) 1/AB
L43 4 ((DICKKOPF-1/AB OR DKK1/AB OR DKK-1/AB) OR ((DICKKOPF/AB (W)
1/AB) OR (DKK/AB (W) 1/AB)))

=> s 142 and 135

L44 1 L42 AND L35

=> d ibib

L44 ANSWER 1 OF 1 PCTFULL COPYRIGHT 2005 Univentio on STN
ACCESSION NUMBER: 2002066509 PCTFULL ED 20020910 EW 200235
TITLE (ENGLISH): TREATMENT INVOLVING DKK-1 OR
 ANTAGONISTS THEREOF
TITLE (FRENCH): TRAITEMENT FAISANT APPEL A DKK-1 OU
 AUX ANTAGONISTES DE DKK-1
INVENTOR(S): DeALMEIDA, Venita I., 3014 Los Prados Avenue, #A116,
 San Mateo, CA 94403, US;
 STEWART, Timothy A., 465 Douglas Street, San Francisco,
 CA 94114, US
PATENT ASSIGNEE(S): GENENTECH, INC., 1 DNA Way, South San Francisco, CA
 94080, US [US, US]
AGENT: HASAK, Janet E.S., GENENTECH, INC., MS 49, 1 DNA Way,
 South San Francisco, CA 94080-4990\$, US
LANGUAGE OF FILING: English
LANGUAGE OF PUBL.: English
DOCUMENT TYPE: Patent
PATENT INFORMATION:

NUMBER	KIND	DATE

WO 2002066509	A2	20020829

DESIGNATED STATES

W: AE AG AL AM AT AU AZ BA BB BG BR BY BZ CA CH CN CO CR
CU CZ DE DK DM DZ EC EE ES FI GB GD GE GH GM HR HU ID
IL IN IS JP KE KG KP KR KZ LC LK LR LS LT LU LV MA MD
MG MK MN MW MX MZ NO NZ OM PH PL PT RO RU SD SE SG SI
SK SL TJ TM TN TR TT TZ UA UG UZ VN YU ZA ZM ZW
RW (ARIPO): GH GM KE LS MW MZ SD SL SZ TZ UG ZM ZW
RW (EAPO): AM AZ BY KG KZ MD RU TJ TM
RW (EPO): AT BE CH CY DE DK ES FI FR GB GR IE IT LU MC NL PT SE
TR
RW (OAPI): BF BJ CF CG CI CM GA GN GQ GW ML MR NE SN TD TG
APPLICATION INFO.: WO 2002-US4573 A 20020215
PRIORITY INFO.: US 2001-60/269,435 20010216

=> d kwic

L44 ANSWER 1 OF 1 PCTFULL COPYRIGHT 2005 Univentio on STN
TIEN TREATMENT INVOLVING DKK-1 OR ANTAGONISTS THEREOF
TIFR TRAITEMENT FAISANT APPEL A DKK-1 OU AUX ANTAGONISTES
DE DKK-1
ABEN Antagonists to Dickkopf-1 (Dkk-1)
proteins are administered in effective amounts to treat disorders involving insulin resistance, such as non-insulin-dependent diabetes mellitus (NIDDM), hypoinsulinemia, and disorders involving muscle atrophy, trauma, or degeneration. Preferably, the antagonists are composed of compositions comprising antibodies directed to Dkk-1 in a pharmaceutically acceptable carrier for use in blocking the effects of Dkk-1. Additionally provided is a method of treating obesity or hyperinsulinemia in a mammal by administering an effective amount of Dkk-1 to a mammal. Also provided are methods of diagnosing insulin resistance, hyper- and hypoinsulinemia, obesity, and related disorders using Dkk-1 as a target and non-human transgenic animals that overexpress <i>dkk-1</i> nucleic acid.
ABFR L'invention concerne un traitement consistant a administrer des antagonistes des proteines Dickkopf-1 (Dkk-1) en quantites efficaces pour traiter les troubles impliquant une resistance insulinaire, tels que le diabete non insulino-dependant (NIDDM), l'hypoinsulinemie et les troubles impliquant une atrophie musculaire, un traumatisme ou une degeneration. Ces antagonistes sont avantageusement composees d'anticorps diriges contre Dkk-1 dans un excipient pharmaceutiquement acceptable et utilises pour bloquer les effets de Dkk-1.
L'invention concerne egalement une methode de traitement de l'obesite ou de l'hyperinsulinemie chez un mammifere, consistant a administrer une quantite efficace de Dkk-1 a un patient. L'invention concerne egalement des methodes permettant de diagnostiquer la resistance insulinaire, l'hyper- et l'hypoinsulinemie, l'obesite et les troubles associes, a l'aide de Dkk-1 comme cible et des animaux transgeniques non humains surexprimant l'acide nucleique <i>dkk-1</i>.
DETD TREATMENT INVOLVING DKK-1 OR ANTAGONISTS THEREOF
Background of the Invention
Field of the Invention
The present invention provides for the diagnosis and treatment of disorders involving . . . hyperinsulinemia and for repairing and regenerating muscle in mammals. More particularly, the present invention relates to the use of Dickkopf- I (Dkk- 1) protein to treat obesity and hyperinsulinemia and to the use of antagonists that bind to Dkk- I and/or neutralize its activity. . .
Dkk-I (WO 99/46281 published Sept. 16, 1999, wherein the Dkk-1 is designated as PRO1008 and is

encoded by DNA57530; WO 00/18914 published April 6, 2000; WO 00/52047 published September 8, 2000; WO. . .

as polycystic ovarian disease, dermatological disorders such as infections, varicose veins, Acanthosis nigricans, and eczema, exercise intolerance, insulin resistance, hypertension, hypercholesterolemia, cholelithiasis, osteoarthritis, orthopedic injury, thromboembolic disease, cancer, and coronary heart disease. Rissanen et al., British Medical Journal, 301.

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Summary of the Invention

Accordingly, antagonists to Dkk-1, such as antibodies, are herein disclosed to be useful in the treatment of insulin resistance associated with, for example, glucose intolerance, . . .

mammal in need thereof an effective amount of an antagonist to Dkk Preferably, the mammal is human, the Dkk-I is human Dkk-1, and/or the human has NIDDM. Also preferred is systemic administration. The antagonist is preferably, an antibody that binds Dkk- 1, and more preferably a monoclonal antibody that binds Dkk- 1, and still more preferably one that neutralizes an insulin-resistance or hypoinsulinemic activity of Dkk Most preferred is a monoclonal antibody prepared from. . .

Preferably, the measuring is carried out using an anti-Dkk-1 antibody, such as a monoclonal antibody, in an immunoassay. Also, preferably such anti-Dkk-1 antibody comprises a label, more preferably a fluorescent label, a radioactive label, or an enzyme label, such as a bioluminescent label. . .

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Additionally provided is a monoclonal antibody preparation prepared by hyperimmunizing mice with tagged Dkk- 1 (preferably purified recombinant polyhistidine-tagged human Dkk-I) diluted in an adjuvant, fusing B-cells from the mice having anti-Dkk-1 antibody titers (preferably high titers) with mouse myeloma cells and obtaining supernatants, harvesting the supernatants, screening the harvested supernatants for antibody production, . . .

a candidate pharmaceutical drug on insulin resistance, hypoinsulinemia, or muscle repair comprising administering said drug to a non-human transgenic animal that overexpresses dkk-1 nucleic acid and determining the effect of the drug on glucose clearance from the blood of said animal, on circulating insulin. . . the animal is a rodent, more preferably a mouse or rat, and most preferably a mouse. In another preferred embodiment, the dkk-1 nucleic acid overexpressed by the animal is under the control of a muscle-specific promoter, and the cDNA is overexpressed in muscle. . .

- (a) a container comprising an antibody that binds Dkk-1;
- (b) a container comprising a standard sample containing Dkk-1; and
- (c) instructions for using the antibody and standard sample to detect

insulin resistance, hypoinsulinemia, hyperinsulinemia, or obesity, wherein either the antibody . . . is detectably labeled or the kit further comprises another container comprising a second antibody that is detectably labeled and binds to the

Dkk-1 or to the antibody that binds Dkk Preferably the anti-Dkk-1 antibody of the kit is a monoclonal antibody, more preferably one that neutralizes an insulin-resistance, hyperinsulinemic, hypoinsulinemic, or obesity activity of Dkk-1.

for detecting the presence or onset of obesity or hyperinsulinemia in a mammal comprising the steps of-
(a) measuring the amount of Dkk-1 in a sample from said mammal; and

(b) comparing the amount determined in step (a) to an amount of Dkk-1 present in a standard sample, a decreased level in the amount of Dkk-1 in step (a) being indicative of obesity or hyperinsulinemia.

Preferably, the measuring is carried out using an anti-Dkk-1 antibody in an immunoassay. Also, preferably the anti-Dkk- I antibody comprises a label. The preferred labels and immunoassays are those as

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set. . .

In a preferred embodiment the Dkk- I is human Dkk- 1 in the kit and it may further comprise a container with a weight-loss agent.

effect of a candidate pharmaceutical drug on obesity or hyperinsulinernia comprising administering said druo, to a non-human binary transgenic animal that expresses dkk-1 nucleic acid and determining the effect of the drug on an obesity-determining property or on the level of insulin in said. . .

The invention also provides a non-human transgenic animal that overexpresses dkk-1 nucleic acid.

method for repairing or regenerating muscle in a mammal comprising administering to the mammal an effective amount of an antagonist to Dkk-1, preferably an antibody that binds to Dkk Preferably, the mammal is human and/or the antibody is a monoclonal antibody.

(a) a container comprising an antagonist toDkk- 1, preferably an antibody that binds Dkk- 1; and
(b) instructions for using the antagonist to repair or regenerate muscle in a mammal.

Figure 2 shows a gel of human Dkk-1 expressed in baculovirus and its clipping.

Figure 3A shows the effects of human Dkk- 1 (dark bars) on basal glucose uptake in L6 muscle cells for 2, 6, and 26 hours. Figures 3B and 3C show, respectively, the effects of human Dkk-1 on basal (light bars) and 30 nM-insulin-stimulated (dark bars) glucose uptake in L6 muscle cells.

shows the effects of human Dkk]1 on basal and insulin-dependent glucose uptake (expressed as percent control) as a function of human Dkk-1 concentration

(nM) upon 48-hour treatment.

Figure 5A-513 show respectively the effect of human Dkk-1 on the incorporation of glucose into glycogen in L6 muscle cells with (dark bars) and without (light bars) insulin for 48. . .

Ficrures 8A-8D show the effect of 40 nM human Dkk-1 (dark bars) on the kinase activities of PDK-I (Fig. 8A), GSK3 P (Fig. 813), S6 kinase (Fig. SC), and Akt (Fig.. . .

Figures 9A and 9B show the effect of human Dkk-1 on levels of basal (light bars) and 30 nM- insulin-stimulated (dark bars) criucose uptake of 3T3 LI cells (adipocytes) after 48-hour. . .

Dkk-I (triangles). Figure I IB shows the insulin levels in the female FVB mice intravenously injected with saline (control), 0.05 mg/kg/day human Dkk-1, and 0.2 mg/kg/day human Dkk. Figure 12A shows the effects of human Dkk-1 on expression of various markers of muscle differentiation in mice injected therewith, with control (light bars) and 0.2 mg/kg/day of human. . .

Figure 17 shows the effect of an anti-human Dkk-1 monoclonal antibody on the Dkk-1-mediated decrease in glucose uptake in L6 cells in the absence and presence of insulin, where the. . . the L6 cells with 40 nM Dkk-I are black bars, and the L6 cells with 40 nM Dkk-I and 0.5 [tg/mL anti-Dkk-1 antibody are dark gray bars on the far right.

An insulin-resistance-treating agent is an agent other than an antagonist to Dkk-1 that is used to treat insulin resistance, such as, for example, hypoglycemic agents. Examples of such treating agents include insulin (one or. . .

As used herein, Dkk- I or Dickkopf- 1 refers to Wnt inhibitor with properties and characteristics described in WO 99/46281 published September 16, 1999 and Glinka et al, Nature,. . .

The expressions, antagonist, antagonist to Dkk-1, and the like within the scope of the present invention are meant to include any molecule that interacts with Dkk-1 and interferes with its function or blocks or neutralizes a relevant activity of Dkk- 1, by whatever means, depending on the indication being treated. It may prevent the interaction between Dkk-1 and one or more of its receptors. Such agents accomplish this effect in various ways. For instance, the class of antagonists that neutralize a Dkk-1 activity will bind to Dkk- I with sufficient affinity and specificity to interfere with Dkk- I as defined below.

An antibody that binds Dkk- 1 is one capable of bindin cr that antigen with sufficient affinity such that the antibody is useful as a therapeutic agent. . . the Dkk Included within this group of antagonists are, for example, antibodies directed against Dkk- I or portions thereof reactive with Dkk-1, the Dkk- I receptor or portions thereof reactive with Dkk-I, or any other licrand that binds to Dkk The term also. . .

neutralize the activity of are used herein to mean, for example, block, prevent, reduce, counteract the activity of, or make the Dkk-1 ineffective by any mechanism. Therefore, the antagonist may prevent a binding event necessary for activation of Dkk-1. By neutralizing antibody is meant an antibody molecule as herein defined that is able to block or significantly reduce an effector function of the Dkk-1. For example, a neutralizing antibody may inhibit or reduce the ability of Dkk-1 to interact with a Dkk-1 receptor. Alternatively, the neutralizing antibody may inhibit or reduce the ability of Dkk-1 to block the Dkk-1 receptor signalling pathway. The neutralizing antibody may also immunospecifically bind to the

Dkk-1 in an immunoassay for Dkk-1 activity such as the ones described herein. It is a characteristic of the neutralizing antibody of . . .

The term non-human transgenic animal that overexpresses dkk-1 nucleic acid herein refers to a non-human animal, such as a rodent, that has included within a plurality of its cells. . .

The term non-human binary transgenic animal that expresses dkk-1 nucleic acid herein refers to a non-human animal, such as a rodent, in which gene expression is controlled by the interaction of Dkk-1 on a

16 target transgene. These interactions are controlled by crossing animal lines (such as rodent, e.g., mouse lines) or by adding or. . .

diagnosing and treating insulin resistance and hypoinsulinemia based on antagonists that bind to, and preferably neutralize, the activity of Dkk

Further, Dkk-1 itself is a useful treatment for obesity and hyperinsulinemia.

Additionally, antagonists to Dkk-1 are further indicated in methods herein for muscle repair and regeneration.

will specifically bind to the protein used for immunization. Alternatively, lymphocytes may be immunized in vitro. Lymphocytes then are fused with myeloma cells using a suitable fusing agent, such as polyethylene glycol, to form a hybridoma cell (Goding, Monoclonal Antibodies: Principles and Practice, pp. . .

in a suitable culture medium that preferably contains one or more substances that inhibit the growth or survival of the unfused, parental

myeloma cells. For example, if the parental myeloma cells lack the enzyme hypoxanthine guanine phosphoribosyl transferase (HGPRT or HPRT), the culture medium for the hybridomas typically will include hypoxanthine, aminopterin,. . .

Preferred myeloma cells are those that fuse efficiently, support stable high-level production of antibody by the selected antibody-producing cells, and are sensitive to. . .

Among these, preferred myeloma cell lines are murine

myeloma lines, such as those derived from MOPC-21 and MPC- I I mouse tumors available from the Salk Institute Cell Distribution Center, . . .

which are then transfected into host cells such as E. coli cells, simian COS cells, Chinese Hamster Ovary (CHO) cells, or myeloma cells that do not otherwise produce antibody protein, to obtain the synthesis of monoclonal antibodies in the recombinant host cells. Review articles. . .

Amino acid sequence modification(s) of the anti-Dkk-1 antibodies described herein are contemplated. For example, it may be desirable to improve the binding affinity and/or other biological properties of the. . . Such modifications include, for example, deletions from, and/or insertions into and/or substitutions of, residues within the amino acid sequences of the anti-Dkk-1 antibody. Any combination of deletion, insertion, and substitution is made to arrive at the final construct, provided that the final construct possesses. . .

. . . or more residues, as well as intrasequence insertions of single or multiple amino acid residues. Examples of terminal insertions include an anti-Dkk-1 antibody with an N-terminal methionyl residue or the antibody fused to a hypoglycemic polypeptide. Other insertional variants of the anti-Dkk- I antibody. . .

preparation by oligonucleotide-mediated (or site-directed) mutagenesis, PCR mutagenesis, or cassette mutagenesis of an earlier prepared variant or a non-variant version of the anti-Dkk- 1 antibody.

serum half-life of the therapeutic antagonist. For example, a soluble immunoglobulin chimera, such as described herein, can be obtained for each specific Dkk-1 antagonist or antagonistic portion thereof, as described in U.S. Pat. No. . .

The preferred dose is about 0.50 mg/kg/day, more preferably about 0.1 to 25 mg/kg/day. More preferred still, when the Dkk- 1 antagonist is administered daily, the intravenous or intramuscular dose for a human is about 0.3 to 10 mg/kg of body weight. . .

Preferred continuous dosing schedules include daily continuous infusion, where Dkk- I antagonist is infused each day, and continuous bolus administration schedules, where Dkk-1 antagonist is administered at least once per day by bolus injection or inhalant or intranasal routes. The invention also encompasses discontinuous. . .

. . . will vary according to the formulation, method of delivery, and clinical needs of the mammal being treated. For example, if the Dkk- 1 antagonist is administered by infusion, administration schedules may comprise a first period of administration followed by a second period in which Dkk-. . .

. . . the administration is by bolus injection, especially bolus injection of a slow-release

formulation, dosing schedules may also be continuous in that Dkk-1 antagonist is administered each day, or may be discontinuous, with first and second periods as described above.

dosing schedule, and route of administration for the treatment of the insulin-resistant or hypoinsulinemic disorder or muscle condition. The containers of Dkk-1 antagonist may be unit doses, bulk packages (e.g., multi-dose packages), or sub-unit doses.

resilient stopper. Ampoules with non-resilient, removable closures (e.g., sealed glass) or resilient stoppers are most conveniently used for injectable forms of Dkk-1 antagonist. Also contemplated are packages for use in combination with a specific device, such as an inhaler, a nasal administration device. . .

One specifically preferred method for administration of Dkk-1 is by subcutaneous infusion, particularly using a metered infusion device, such as a pump. Such pump can be reusable or disposable, . . .

Therapeutic formulations of Dkk-1 suitable for storage include mixtures of the Dkk-1 having the desired degree of purity with pharmaceutically acceptable carriers, excipients, or stabilizers (Remington's Pharmaceutical Sciences 16th edition, Osol, A. Ed. (1980)), . . . are described in WO 97/04801. These compositions comprise Dkk-1 containing from about 0.1 to 90% by weight of the active Dkk-1, preferably in a soluble form, and more generally from about 10 to 30%.

methods. In addition, sustained-release preparations may be prepared. Suitable examples of sustained-release preparations include semipermeable matrices of solid hydrophobic polymers containing the Dkk-1, which matrices are in the form of shaped articles, e.g., films, or microcapsules. Examples of sustained-release matrices include polyesters, hydrogels (for example, . . .

The Dkk-1 can be joined to a carrier protein or PEG or POG or other molecule of this nature to increase its serum half-life, . . .

For treatment of hyperinsulinemia, the administration of Dkk-1 may occur in conjunction with, for example, diazoxide (see, for example, Shaer, Nephron, 89: 337-339 (2001)).

For treatment of obesity, the administration of Dkk-1 may occur without, or may be imposed with, a dietary restriction such as a limit in daily food or calorie intake, as is desired for the individual patient. In addition, the Dkk-1 is appropriately administered in combination with other treatments for combatting or preventing obesity, known herein as weight-loss agents. Substances useful for. . .

These weight-loss adjunctive agents and diazoxide may be administered at the same time as, before, or after the administration of the Dkk-1 and can be administered by the same or a different administration route than the Dkk-1 is administered.

The dosages of Dkk-1 administered to an obese or hyperinsulinemic mammal will be determined by the physician in the light of the relevant circumstances, including the condition of the mammal, the type of

Dkk-1, and the chosen route of administration. The dosage is preferably at a sufficiently low level as not to cause insulin-resistance, and. . . . The preferred dose is about 0.50 32

mg/kg/day, more preferably about 0.1 to 25 mg/kg/day. More preferred still, when the Dkk-1 is administered daily, the intravenous or intramuscular dose for a human is about 0.3 to 10 mc.,r/kg of body weight per. . . .

Dkk-1 is administered by infusion, administration schedules may comprise a first period of administration followed by a second period in which Dkk-1 is not administered that is greater than, equal to, or less than the first period.

also provides kits for the treatment of obesity or hyperinsulinemia. The kits of the invention comprise one or more containers of Dkk-1, preferably human Dkk-1, in combination with a set of instructions, generally written instructions, relating to the use and dosage of Dkk-1 for the. . . .

Dkk-1 may be packaged in any convenient, appropriate packaging. For example, if the Dkk-1 is a freeze-dried formulation, an ampoule with a resilient stopper is normally used, so that the drug may be easily reconstituted by. . . .

In one embodiment, one or more of the anti-Dkk-1 antibodies used in the assay is labeled; in another embodiment, a first is unlabeled, and a labeled, second antibody is used. . . .

I antibody need not be labeled, and the presence thereof can be detected using a labeled antibody which binds to the Dkk-1 antibody.

In the assays of the present invention, an antigen such as Dkk-1, or an antibody is preferably bound to a solid phase support or carrier. By solid phase support or carrier is intended. . . .

a solid phase matrix, preferably a microplate. The sample is brought in contact with the Ab I-coated matrix such that any Dkk-1 in the sample to which AM is specific binds to the solid-phase AbI. Unbound sample components are removed by washing. An. . . .

the diagnostic assay. For instance, such a kit can comprise an antibody or antibodies, preferably a pair of antibodies to the Dkk-1 anti cren that preferably do not compete for the same binding site on the antigen. In a specific embodiment, Dkk-1 may be pre-adsorbed to the solid phase matrix. The kit preferably contains the other necessary washing reagents well-known in the art. . . . the art, and some are exemplified below. The kit can optionally also comprise a Dkk-1 standard; ie., an amount of purified Dkk-1 corresponding to a normal amount of Dkk-1 in a standard sample.

In one aspect, a kit comprises in more than one container: an antibody that binds Dkk-1, which can be coated on a solid-phase carrier, e.g., a microtiter plate, a standard sample containing Dkk-1, and instructions for use in detection, wherein the antibody that binds Dkk-I is detectably labeled or the kit further comprises an . . .

cDNA such as inurine cDNA encoding Dkk- I or an appropriate sequence thereof can be used to clone genomic DNA encoding Dkk-1 in accordance with established techniques, and the genomic sequences are used to generate trans crenic animals that contain cells that express DNA encoding Dkk- 1.

transgene incorporation with tissue-specific enhancers, which results in targeted overexpression of Dkk Transgenic animals that include a copy of a transgene encoding

Dkk-1 introduced into the crerm line of the animal at an embryonic stage can be used to examine the effect of increased. . .

a probe that is complementary to at least a portion of the transgene. Western blot analysis

using an antibody against the Dkk-1 encoded by the transcrene may be employed as an alternative or additional method for screenina for the presence of the transcrene. . .

specific type of cell. The most preferred such control element herein is a muscle-specific promoter that enables overexpression of the dkk-1 nucleic acid (e.g., cDNA) in muscle tissue. An example of such promoter is that described in Example I below or that. . .

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In another facet, non-human binary transgenic animals having altered dkk-1 nucleic acid expression can be used to screen candidate drugs as set forth above, such as for their ability to reduce. . .

Example 1

Effects of Dkk-1 itz vivo and in vitro

Materials and Methods

L6 Cell culture

L6 myoblasts were proliferated in growth medium, composed of MEM alpha (Gibco-BRL). . . differentiation medium at confluence (MEM alpha with 2% fetal calf serum). Cells were grown in this medium for 3-9 days and for

Dkk-1 treatments longer than 28 hours, dkk--1 (Krupnik et al., supra; WO 99/46281; DNA encoding PRO1008) was added to this medium. Treatments. . .

Expression of Recombinant Dkk-I

The human homolog of Dkk-1 (hDkk-1) was expressed as a C-terminal 8X His tag fusion (see

Krupnik et al., supra; and WO 99/46281, where PRO1008 is Dkk-1) in baculovirus and purified by nickel affinity column chromatography. The identity of purified protein was verified by N-terminal sequence analysis. The purified. . .

Glycogen Synthesi

Glycogen synthesis was determined as [14 Clglucose incorporation into

glycooren. Control L6 cells and cells treated with dkk-1 were incubated for 2 hours in serum-free MEM alpha containing [3 H]-glucose (5 mM glucose; 1.25 pCi/n-d) with or without. . .

Chem., 253: 7570-7578 (1978)). Differentiated cells were treated with Dkk-I at 72 hours after the induction of differentiation. For effect of Dkk-1 on 3T3L1 cell differentiation, Dkk-I was added to the medium at a concentration of 40 nM during the initiation of differentiation. . .

3' to the pRK splice donor/acceptor site that was preceded by the myosin light-chain promoter (Shani, Nature, 314: 283-286 (1985)). The dkk-1 cDNA was followed by the splice donor/acceptor sites present between the fourth and fifth exons of the human growth hormone gene (Stewart. . .

When expressed in baculovirus, the human Dkk-1 protein was clipped internally to give a 16-kDa cleavage product. In the gel shown in Fig. 2, band (a) corresponds to.

The Dkk-1 effects of glucose uptake are independent of the differentiation state of the cells and can be seen even in cells that. . . uptake are dose-dependent. Fig. 4B shows that the decrease in basal and insulin-dependent glucose uptake is seen upon 48-hour treatment with Dkk-1 at concentrations as low as 10 nM.

regulated the expression of genes in the insulin signaling pathway in L6 muscle cells. In particular, as shown in Fig. 7, Dkk-1 treatment increased the expression of the p85 subunit of phosphoinositide 3-kinase significantly (8.3 fold) following 48-hour treatment, but did not significantly affect. . .

Dkk- I in mice resulted in impaired glucose tolerance and reduced insulin production. Specifically, to confirm the *in vivo* effects of Dkk-1 seen in transgenic mice, female FVB mice were injected intravenously with Dkk-1 for 8 days (single daily injection of 0.05 and 0.2 mg/kg/day). The effects of Dkk- 1 on glucose tolerance were measured 48 hours and 8 days after the start of injection. Glucose tolerance was unaffected with 48. . .

Overexpression of Dkk-1 in mice affected growth, body composition, and metabolism. Particularly, Transcrenic FVB mice overexpressing the dkk-1 transgene under control of the MLC promoter were generated (Shani, *supra*). Body weights of control and transgenic animals were followed over. . .

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Table 2
Control Control Dkk-I Dkk-1
Regular diet Regular diet transgenic transgenic
Physiological Parameter (males, n=8) (females, n=4) Regular diet Regular diet
males, n=4) (females, n=8)
Body Weight at 16. . .

signaling inhibits adipogenesis. To determine whether Dkk-I affected body composition, some animals were placed on a high-fat diet for 24 weeks. Dkk-

1 transgenic animals on a high-fat diet also showed significantly reduced body weights than their wild-type littermates (Fig. 15A), with comparable reduction. . .

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Table 3

Control Control Dkk-1 TG Dkk-1

TG

High-fat diet High-fat diet High-fat diet High-fat diet

eter (m=12) (f=8) m=6) (f=5)

Body Weight at 16 of

40.3 ± 6.6 34.7 ±. . .

diabetes, can be affected by expression levels, phosphorylation, and activity of proteins in the insulin- signaling pathway. Therefore, the effects of Dkk-1 in muscle both in vivo and in vitro were investigated.

animals also had reduced levels of serum insulin, although no effects were seen in the serum insulin levels in transgenic mice. Dkk-1 reduced the basal and insulin-stimulated glucose uptake in L6 cells through inhibition of Akt, a key intermediate in the insulin-signaling pathway.

These effects of Dkk-1 were seen only after 18 hrs of exposure to Dkk-1.

size with a proportional decrease in the weight of various organs. Without being limited to any one theory, these effects of Dkk-1 are likely to be mediated through the reduction in insulin (and likely IGF-1)-stimulated Akt activity. Direct evidence for this comes from studies. . .

Chem., 276: 19664-19671 (2001)). Alternatively, without limitation to any one theory, the reduced growth rate in dkk-1 transgenic animals could be a secondary effect of the reduced glucose uptake and consequent alteration in nutrient availability and metabolic rate. . .

Primary 3T3LI preadipocytes were stimulated to differentiate in the presence or absence of Dkk-1, cells were collected at different days after the start of differentiation, and the transcripts analysed for expression levels of markers of adipocyte differentiation such as AP2, PPAR γ , CEB P(x, and FAS. Dkk-1 treatment did not alter levels of FAS and AP2; however, PPAR γ levels were about 2-fold reduced in Dkk-1- treated cells and C/EBP α levels. . .

adipose tissue mass and are up-regulated by Akt (Barthel et al., Endocrinology -3562 (1997)). The reduced levels of circulating leptin in dkk-1

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transgenic animals could be a direct effect of decreased adipose mass and/or decreased Akt activity in adipose tissue, without being limited. . .

A significant reduction in the levels of secreted insulin was observed herein following 8 days of Dkk-1 injection, and smaller effects in transgenic animals overexpressing dkk-1 in the muscle. Without being

limited to any one theory, the stronger effects in injected animals could be a result of. . . there may be smaller differences in insulin levels either due to compensatory mechanisms or due to a more localized effect of Dkk-1 in the muscle. Since Akt is known to stimulate islet cell proliferation and insulin production, and since the data herein show for the first time that Dkk-1-injected and transgenic mice have lower insulin levels, an antagonist to Dkk-1 is now found useful in treating hypoinsulinemia, and conversely, Dkk-1 itself is found useful in treating hyperinsulinemia.

in L6 muscle cells as well as in transgenic mice overexpressing the protein in muscle. Treatment of muscle cells with Dkk-1 resulted in a decrease in the basal and insulin-stimulated glucose uptake. This effect was observed following both short-term and long-term treatment,

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suggesting, without being limited to any one theory, that Dkk-1 may affect both the activity as well as the expression levels of proteins in the insulin signaling pathway. Consistent with this. . .

obesity and hyperinsulinemia, as well as being useful as a diagnostic marker in assays for such conditions. Also, an antagonist to Dkk-1 is expected to inhibit the progression of the diabetes phenotype in transgenic animal models disclosed in U.S. Pat. No. 6,187,991.

Example 2

Development of Anti-Dkk-1 Monoclonal Antibodies

Five female Balb/c mice (Charles River Laboratories, Wilmington, DE) were hyperimmunized with purified recombinant polyhistidine-tagged (HIS8) human Dkk-1 expressed. . . used for each animal, administered via footpad. After five injections, B-cells from the lymph nodes of the five mice, demonstrating high anti-Dkk-1 antibody titers, were fused with mouse myeloma cells (X63.Ag8.653; American Type Culture Collection, Manassas, VA) using the protocols described in Kohler and Milstein, *supra*, and Hongo et al., . .

All the seven antibody preparations bound Dkk-1 in Western immunoblots.

L6 cells were differentiated and treated for 48 hours in the absence of Dkk-1 (control) or in the presence of 40 nM Dkk-1 (plus or minus anti-Dkk-1 antibody 1G1.2D12.2D1 1 (ATCC No. PTA-3086) in an amount of 0.5 ttg/mL). Basal and insulin-stimulated glucose uptake in the L6 cells. . .

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Designation ATCC Dep. No. Deposit Date

DKK1.MAB3139.8CI 1.2GI 1. IDI PTA-3084 February 21, 2001

DKK1.MAB3143.4C7.2H10.2GI PTA-3085 February 21, 2001

DKKLMAB3142. I G1.21) 12.2131 1 PTA-3086 February 21, 2001

DKK1.MAB3141.5B12.2C5.2A5 PTA-3087 February 21, 2001

DKKLMAB313 8.7C 1 1 16.2AS PTA-3088 February 21, 2001

DKK1.MAB3140.7B2.2A6.2H4 PTA-3089 February 21, 2001

DKK1.MAB3144.5A2.2A8.1C3 PTA-3097 February 21, 2001

This deposit was made under the provisions of the Budapest Treaty on the International Recognition

of the Deposit. . .

CLMEN. . . insulin resistance or hypoinsulinemia in mammals comprising administering to a mammal in need thereof an effective amount of an antagonist to Dickkopf- 1 (Dkk- 1).

4 The method of claim 1 wherein the antagonist is an antibody that binds Dkk- 1.

5 . The method of claim 4 wherein the antibody is a monoclonal antibody.

presence or onset of insulin resistance or hypoinsulinemia in a mammal comprising the steps of:

(a) measuring the amount of Dickkopf- I (Dkk- 1) in a sample from said mammal; and

(b) comparing the amount determined in step (a) to an amount of Dkk- I.

12 The method of claim 1 I wherein the anti-Dkk- 1 antibody comprises a label.

16 The method of claim 10 wherein the mammal is human and human Dkk- 1 is being measured.

17 A kit for treating insulin resistance or hypoinsulinemia, said kit comprising:

(a) a container comprising an antagonist to Dkk-1; and

(b) instructions for using the antagonist to treat insulin resistance or hypoinsulinemia.

18 The kit of claim 17 wherein the antagonist is an antibody that binds Dkk- 1

20 The kit of claim 18 wherein the antibody binds human Dkk- 1.

26 A method of treating obesity or hyperinsulinemia in mammals comprising administering to a mammal in need thereof an effective amount of Dickkopf-I (Dkk-1).

for detecting the presence or onset of obesity or hyperinsulinemia in a mammal comprising the steps of.

(a) measuring the amount of Dickkopf-1 (Dkk]1) in a sample from said mammal; and

(b) comparing the amount determined in step (a) to an amount of Dkk-1 present in a standard sample, a decreased level in the amount of Dkk-1 in step (a) being indicative of obesity or hyperinsulinemia.

36 A kit for treating obesity or hyperinsulinemia, said kit comprising:

(a) a container comprising Dkk- 1; and

(b) instructions for using the Dkk- I to treat obesity or hyperinsulinemia.

the presence or onset of insulin resistance, hyperinsulinemia, hypoinsulinemia, or obesity, said kit comprising:

(a) a container comprising an antibody that binds Dickkopf- 1 (Dkk-1);

(b) a container comprising a standard sample containing Dkk- 1; and

(c) instructions for using the antibody and standard sample to detect insulin resistance,

hyperinsulinemia, hypoinsulinemia, or obesity, wherein either the antibody. . .

41 The kit of claim 39 wherein the Dkk-1 is human Dkk-1 and the kit is for detecting non-insulin dependent diabetes or obesity.

53

. A method for repairing or regenerating muscle in a mammal comprising.

47 A monoclonal antibody preparation prepared by hyperimmunizing mice with tagged Dkk-1 diluted in an adjuvant, fusing B-cells from the mice having anti-Dkk-I antibody titers with mouse myeloma cells and obtaining supernatants, harvesting the supernatants, screening the harvested supernatants for antibody production, injecting positive clones showing the highest immunobinding after. . .

=> d his

(FILE 'HOME' ENTERED AT 13:01:12 ON 25 JUL 2005)

FILE 'MEDLINE' ENTERED AT 13:01:25 ON 25 JUL 2005

L1 3942 S WNT
L2 244 S L1 (S) ANTAGON?
L3 553450 S OSTEO? OR BONE
L4 70 S L3 AND L2
L5 22597 S MULTIPLE MYELOMA
L6 1 S L5 AND L4
L7 1 S L2 AND L5
L8 31029 S MYELOMA
L9 1 S L8 AND L2
L10 451 S L1 AND L3
L11 7 S L10 AND L5
L12 1 S L11 NOT PY>2002
L13 70 S (DICKKOPF () 1) OR (DKK () 1)
L14 2 S L13 AND L11
L15 19 S L13 AND L3
L16 14 S L15 AND EXPRESS?
L17 6 S L16 NOT PY>2002

FILE 'CAPLUS' ENTERED AT 13:06:53 ON 25 JUL 2005

L18 4365 S WNT
L19 273 S L1 (S) ANTAGON?
L20 .273 S L18 (S) ANTAGON?
L21 16913 S MYELOMA
L22 5 S L20 AND L21
L23 123 S (DICKKOPF () 1) OR (DKK () 1)
L24 155 S DICKKOPF-1 OR DKK1
L25 170 S L23 OR L24
L26 61795 S OSTEO?
L27 32 S L26 AND L25
L28 7 S L27 AND L21

FILE 'PCTFULL' ENTERED AT 13:10:21 ON 25 JUL 2005

L29 1307 S WNT
L30 161 S L29 (S) ANTAG?
L31 46 S (DICKKOPF () 1) OR (DKK () 1)
L32 62 S DICKKOPF-1 OR DKK1 OR DKK-1
L33 62 S L32 OR L31
L34 27031 S OSTEO?
L35 59451 S L34 OR BONE
L36 87552 S CANCER? OR TUMOR? OR NEOPLAS?

L37 14570 S MYELOMA
L38 39 S L33 AND L34
L39 18 S L38 AND L37
L40 8 S L39 NOT PY>2002
L41 10 S L33/CLM
L42 1 S L41 AND L40
L43 4 S L33/AB
L44 1 S L42 AND L35

=> s d ibib
966935 D
18 IBIB
L45 0 D IBIB
(D(W)IBIB)

=> d 144 ibib

L44 ANSWER 1 OF 1 PCTFULL COPYRIGHT 2005 Univentio on STN
ACCESSION NUMBER: 2002066509 PCTFULL ED 20020910 EW 200235
TITLE (ENGLISH): TREATMENT INVOLVING DKK-1 OR
ANTAGONISTS THEREOF
TITLE (FRENCH): TRAITEMENT FAISANT APPEL A DKK-1 OU
AUX ANTAGONISTES DE DKK-1
INVENTOR(S): DeALMEIDA, Venita I., 3014 Los Prados Avenue, #A116,
San Mateo, CA 94403, US;
STEWART, Timothy A., 465 Douglas Street, San Francisco,
CA 94114, US
PATENT ASSIGNEE(S): GENENTECH, INC., 1 DNA Way, South San Francisco, CA
94080, US [US, US]
AGENT: HASAK, Janet E.S., GENENTECH, INC., MS 49, 1 DNA Way,
South San Francisco, CA 94080-4990\$, US
LANGUAGE OF FILING: English
LANGUAGE OF PUBL.: English
DOCUMENT TYPE: Patent
PATENT INFORMATION:
NUMBER KIND DATE

WO 2002066509 A2 20020829
DESIGNATED STATES
W: AE AG AL AM AT AU AZ BA BB BG BR BY BZ CA CH CN CO CR
CU CZ DE DK DM DZ EC EE ES FI GB GD GE GH GM HR HU ID
IL IN IS JP KE KG KP KR KZ LC LK LR LS LT LU LV MA MD
MG MK MN MW MX MZ NO NZ OM PH PL PT RO RU SD SE SG SI
SK SL TJ TM TN TR TT TZ UA UG UZ VN YU ZA ZM ZW
GH GM KE LS MW MZ SD SL SZ TZ UG ZM ZW
RW (ARIPO): AM AZ BY KG KZ MD RU TJ TM
RW (EAPO): AT BE CH CY DE DK ES FI FR GB GR IE IT LU MC NL PT SE
TR
RW (OAPI): BF BJ CF CG CI CM GA GN GQ GW ML MR NE SN TD TG
APPLICATION INFO.: WO 2002-US4573 A 20020215
PRIORITY INFO.: US 2001-60/269,435 20010216

=> file dissab
COST IN U.S. DOLLARS
FULL ESTIMATED COST

SINCE FILE ENTRY	TOTAL SESSION
16.18	62.30

FILE 'DISSABS' ENTERED AT 13:16:14 ON 25 JUL 2005
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=> s dickkopf-1 or DKK1 or DKK-1
2 DICKKOPF
1 DICKKOPFS
3 DICKKOPF
(DICKKOPF OR DICKKOPFS)
354082 1
2 DICKKOPF-1
(DICKKOPF(W) 1)
2 DKK1
3 DKK
1 DKKS
3 DKK
(DKK OR DKKS)
354082 1
2 DKK-1
(DKK(W) 1)
L46 4 DICKKOPF-1 OR DKK1 OR DKK-1

=> s osteo?
L47 3245 OSTEOT?

=> s 147 and 146
L48 0 L47 AND L46

=> s 146 and myeloma
547 MYELOMA
32 MYELOMAS
567 MYELOMA
(MYELOMA OR MYELOMAS)
L49 0 L46 AND MYELOMA

=> d his

(FILE 'HOME' ENTERED AT 13:01:12 ON 25 JUL 2005)

FILE 'MEDLINE' ENTERED AT 13:01:25 ON 25 JUL 2005
L1 3942 S WNT
L2 244 S L1 (S) ANTAGON?
L3 553450 S OSTEO? OR BONE
L4 70 S L3 AND L2
L5 22597 S MULTIPLE MYELOMA
L6 1 S L5 AND L4
L7 1 S L2 AND L5
L8 31029 S MYELOMA
L9 1 S L8 AND L2
L10 451 S L1 AND L3
L11 7 S L10 AND L5
L12 1 S L11 NOT PY>2002
L13 70 S (DICKKOPF () 1) OR (DKK () 1)
L14 2 S L13 AND L11
L15 19 S L13 AND L3
L16 14 S L15 AND EXPRESS?
L17 6 S L16 NOT PY>2002

FILE 'CAPLUS' ENTERED AT 13:06:53 ON 25 JUL 2005
L18 4365 S WNT
L19 273 S L1 (S) ANTAGON?
L20 273 S L18 (S) ANTAGON?

L21 16913 S MYELOMA
L22 5 S L20 AND L21
L23 123 S (DICKKOPF () 1) OR (DKK () 1)
L24 155 S DICKKOPF-1 OR DKK1
L25 170 S L23 OR L24
L26 61795 S OSTEO?
L27 32 S L26 AND L25
L28 7 S L27 AND L21

FILE 'PCTFULL' ENTERED AT 13:10:21 ON 25 JUL 2005
L29 1307 S WNT
L30 161 S L29 (S) ANTAG?
L31 46 S (DICKKOPF () 1) OR (DKK () 1)
L32 62 S DICKKOPF-1 OR DKK1 OR DKK-1
L33 62 S L32 OR L31
L34 27031 S OSTEO?
L35 59451 S L34 OR BONE
L36 87552 S CANCER? OR TUMOR? OR NEOPLAS?
L37 14570 S MYELOMA
L38 39 S L33 AND L34
L39 18 S L38 AND L37
L40 8 S L39 NOT PY>2002
L41 10 S L33/CLM
L42 1 S L41 AND L40
L43 4 S L33/AB
L44 1 S L42 AND L35
L45 0 S D IBIB

FILE 'DISSABS' ENTERED AT 13:16:14 ON 25 JUL 2005
L46 4 S DICKKOPF-1 OR DKK1 OR DKK-1
L47 3245 S OSTEO?
L48 0 S L47 AND L46
L49 0 S L46 AND MYELOMA

	SINCE FILE ENTRY	TOTAL SESSION
COST IN U.S. DOLLARS		
FULL ESTIMATED COST	0.82	63.12

FILE 'PCTFULL' ENTERED AT 13:17:23 ON 25 JUL 2005
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FILE LAST UPDATED: 19 JUL 2005 <20050719/UP>
MOST RECENT UPDATE WEEK: 200528 <200528/EW>
FILE COVERS 1978 TO DATE

>>> IMAGES ARE AVAILABLE ONLINE AND FOR EMAIL-PRINTS <<<

=> s 143 and 135
L50 4 L43 AND L35

=> d ibib 1-4

L50 ANSWER 1 OF 4 PCTFULL COPYRIGHT 2005 Univentio on STN
ACCESSION NUMBER: 2005049640 PCTFULL ED 20050607 EW 200522
TITLE (ENGLISH): RHESUS MONKEY DICKKOPF-1, NUCLEOTIDES ENCODING SAME,
AND USES THEREOF
TITLE (FRENCH): PROTEINE DICKKOPF-1 DE SINGE RHESUS, NUCLEOTIDES CODANT
LADITE PROTEINE, ET PROCEDES D'UTILISATION
INVENTOR(S): HARADA, Shun-ichi, 126 East Lincoln Avenue, Rahway, NJ
07065-0907, US [JP, US];
KASPARCOVA, Viera, 126 East Lincoln Avenue, Rahway, NJ
07065-0907, US [CZ, US];
GLANTSCHNIG, Helmut, 126 East Lincoln Avenue, Rahway,
NJ 07065-0907, US [AT, US]

PATENT ASSIGNEE(S) : MERCK & CO., INC., 126 East Lincoln Avenue, Rahway, NJ 07065-0907, US [US, US], for all designates States except US;
 HARADA, Shun-ichi, 126 East Lincoln Avenue, Rahway, NJ 07065-0907, US [JP, US], for US only;
 KASPARCOVA, Viera, 126 East Lincoln Avenue, Rahway, NJ 07065-0907, US [CZ, US], for US only;
 GLANTSCHNIG, Helmut, 126 East Lincoln Avenue, Rahway, NJ 07065-0907, US [AT, US], for US only
 MERCK & CO., INC.\$, 126 East Lincoln Avenue, Rahway, NJ 07065-0907\$, US

AGENT:

LANGUAGE OF FILING: English
 LANGUAGE OF PUBL.: English
 DOCUMENT TYPE: Patent
 PATENT INFORMATION:

NUMBER	KIND	DATE
WO 2005049640	A2	20050602

DESIGNATED STATES
 W:
 AE AG AL AM AT AU AZ BA BB BG BR BW BY BZ CA CH CN CO
 CR CU CZ DE DK DM DZ EC EE EG ES FI GB GD GE GH GM HR
 HU ID IL IN IS JP KE KG KP KR KZ LC LK LR LS LT LU LV
 MA MD MG MK MN MW MX MZ NA NI NO NZ OM PG PH PL PT RO
 RU SC SD SE SG SK SL SY TJ TM TN TR TT TZ UA UG US UZ
 VC VN YU ZA ZM ZW
 BW GH GM KE LS MW MZ NA SD SL SZ TZ UG ZM ZW
 AM AZ BY KG KZ MD RU TJ TM
 AT BE BG CH CY CZ DE DK EE ES FI FR GB GR HU IE IS IT
 LU MC NL PL PT RO SE SI SK TR
 BF BJ CF CG CI CM GA GN GQ GW ML MR NE SN TD TG
 WO 2004-US38489 A 20041112
 PRIORITY INFO.: US 2003-60/520,708 20031117

L50 ANSWER 2 OF 4
 ACCESSION NUMBER: PCTFULL COPYRIGHT 2005 Univentio on STN 2004053063 PCTFULL ED 20040630 EW 200426
 TITLE (ENGLISH): MOLECULAR DETERMINANTS OF MYELOMA BONE DISEASE AND USES THEREOF
 TITLE (FRENCH): DETERMINANTS MOLECULAIRES DE MALADIE OSSEUSE DE TYPE MYELOME ET UTILISATIONS DE CEUX-CI
 INVENTOR(S): SHAUGHNESSY, John, D., 4317 Old Oak Drive, Little Rock, AR 72222, US
 PATENT ASSIGNEE(S): THE BOARD OF TRUSTEES OF THE UNIVERSITY OF ARKANSAS, 2404 North University Avenue, Little Rock, AR 72207-3608, US [US, US]
 AGENT: ADLER, Benjamin, A.\$, Adler & Associates, 8011 Candle Lane, Houston, TX 77071\$, US

LANGUAGE OF FILING: English
 LANGUAGE OF PUBL.: English
 DOCUMENT TYPE: Patent
 PATENT INFORMATION:

NUMBER	KIND	DATE
WO 2004053063	A2	20040624

DESIGNATED STATES
 W:
 AL AM AT AU AZ BA BB BG BR BY CA CH CN CU CZ DE DK EE
 ES FI GB GD GE GH GM HR HU ID IL IN IS JP KE KG KP KR
 KZ LC LK LR LS LT LU LV MD MG MK MN MW MX NO NZ PL PT
 RO RU SD SE SG SK SL TJ TM TR TT UA UG UZ VN YU ZA ZW
 BW GH GM KE LS MW MZ SD SL SZ TZ UG ZM ZW
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 AT BE BG CH CY CZ DE DK EE ES FI FR GB GR HU IE IT LU
 MC NL PT RO SE SI SK TR
 BF BJ CF CG CI CM GA GN GQ GW ML MR NE SN TD TG
 WO 2003-US38372 A 20031204
 PRIORITY INFO.: US 2002-60/431,040 20021205

L50 ANSWER 3 OF 4 PCTFULL COPYRIGHT 2005 Univentio on STN
ACCESSION NUMBER: 2002092015 PCTFULL ED 20021210 EW 200247
TITLE (ENGLISH): REAGENTS AND METHODS FOR MODULATING DKK-MEDIATED
INTERACTIONS
TITLE (FRENCH): REACTIFS ET PROCEDES DESTINES A MODULER DES
INTERACTIONS INDUITES PAR DKK
INVENTOR(S): ALLEN, Kristina, 11 Oliver Lane, Hopkinton, MA
01748-3108, US [US, US];
ANISOWICZ, Anthony, 50 Upham Street, West Newton, MA
02465, US [US, US];
BHAT, Bheem, M., 1214 Mayapple Lane, West Chester, PA
19380, US [IN, US];
DAMAGNEZ, Veronique, 125 Water Street, Framingham, MA
01701, US [FR, US];
ROBINSON, John, Allen, 23 Webb Road, Downingtown, PA
19335, US [US, US];
YAWORSKY, Paul, J., 13 Hobart Lane, Rockland, MA 02370,
US [US, US]
PATENT ASSIGNEE(S): GENOME THERAPEUTICS CORPORATION, 100 Beaver Street,
Waltham, MA 02453, US [US, US], for all designates
States except US;
WYETH, Five Giralda Farms, Madison, NJ 07928, US [US,
US], for all designates States except US;
ALLEN, Kristina, 11 Oliver Lane, Hopkinton, MA
01748-3108, US [US, US], for US only;
ANISOWICZ, Anthony, 50 Upham Street, West Newton, MA
02465, US [US, US], for US only;
BHAT, Bheem, M., 1214 Mayapple Lane, West Chester, PA
19380, US [IN, US], for US only;
DAMAGNEZ, Veronique, 125 Water Street, Framingham, MA
01701, US [FR, US], for US only;
ROBINSON, John, Allen, 23 Webb Road, Downingtown, PA
19335, US [US, US], for US only;
YAWORSKY, Paul, J., 13 Hobart Lane, Rockland, MA 02370,
US [US, US], for US only
AGENT: REA, Teresa, Stanek\$, Burns, Doane, Swecker & Mathis
L.L.P., P.O. Box 1404, Alexandria, VA 22313-1404\$, US
LANGUAGE OF FILING: English
LANGUAGE OF PUBL.: English
DOCUMENT TYPE: Patent
PATENT INFORMATION:
NUMBER KIND DATE

WO 2002092015 A2 20021121
DESIGNATED STATES
W: AE AG AL AM AT AU AZ BA BB BG BR BY BZ CA CH CN CO CR
CU CZ DE DK DM DZ EC EE ES FI GB GD GE GH GM HR HU ID
IL IN IS JP KE KG KP KR KZ LC LK LR LS LT LU LV MA MD
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RW (EAPO): AT BE CH CY DE DK ES FI FR GB GR IE IT LU MC NL PT SE
TR
RW (OAPI): BF BJ CF CG CI CM GA GN GQ GW ML MR NE SN TD TG
APPLICATION INFO.: WO 2002-US15982 A 20020517
PRIORITY INFO.: US 2001-60/291,311 20010517
US 2002-60/353,058 20020201
US 2002-60/361,293 20020304

L50 ANSWER 4 OF 4 PCTFULL COPYRIGHT 2005 Univentio on STN
ACCESSION NUMBER: 2002066509 PCTFULL ED 20020910 EW 200235
TITLE (ENGLISH): TREATMENT INVOLVING DKK-1 OR ANTAGONISTS THEREOF
TITLE (FRENCH): TRAITEMENT FAISANT APPEL A DKK-1 OU AUX ANTAGONISTES DE

DKK-1

INVENTOR(S): DeALMEIDA, Venita I., 3014 Los Prados Avenue, #A116,
San Mateo, CA 94403, US;
STEWART, Timothy A., 465 Douglas Street, San Francisco,
CA 94114, US

PATENT ASSIGNEE(S): GENENTECH, INC., 1 DNA Way, South San Francisco, CA
94080, US [US, US]

AGENT: HASAK, Janet E.S., GENENTECH, INC., MS 49, 1 DNA Way,
South San Francisco, CA 94080-4990\$, US

LANGUAGE OF FILING: English

LANGUAGE OF PUBL.: English

DOCUMENT TYPE: Patent

PATENT INFORMATION:

	NUMBER	KIND	DATE
	WO 2002066509	A2	20020829

DESIGNATED STATES

W: AE AG AL AM AT AU AZ BA BB BG BR BY BZ CA CH CN CO CR
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IL IN IS JP KE KG KP KR KZ LC LK LR LS LT LU LV MA MD
MG MK MN MW MX MZ NO NZ OM PH PL PT RO RU SD SE SG SI
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GH GM KE LS MW MZ SD SL SZ TZ UG ZM ZW

RW (ARIPO): AM AZ BY KG KZ MD RU TJ TM

RW (EAPO): AT BE CH CY DE DK ES FI FR GB GR IE IT LU MC NL PT SE
TR

RW (OAPI): BF BJ CF CG CI CM GA GN GO GW ML MR NE SN TD TG

APPLICATION INFO.: WO 2002-US4573 A 20020215

PRIORITY INFO.: US 2001-60/269,435 20010216

=> d his

(FILE 'HOME' ENTERED AT 13:01:12 ON 25 JUL 2005)

FILE 'MEDLINE' ENTERED AT 13:01:25 ON 25 JUL 2005

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L2 244 S L1 (S) ANTAGON?
L3 553450 S OSTEO? OR BONE
L4 70 S L3 AND L2
L5 22597 S MULTIPLE MYELOMA
L6 1 S L5 AND L4
L7 1 S L2 AND L5
L8 31029 S MYELOMA
L9 1 S L8 AND L2
L10 451 S L1 AND L3
L11 7 S L10 AND L5
L12 1 S L11 NOT PY>2002
L13 70 S (DICKKOPF () 1) OR (DKK () 1)
L14 2 S L13 AND L11
L15 19 S L13 AND L3
L16 14 S L15 AND EXPRESS?
L17 6 S L16 NOT PY>2002

FILE 'CAPLUS' ENTERED AT 13:06:53 ON 25 JUL 2005

L18 4365 S WNT
L19 273 S L1 (S) ANTAGON?
L20 273 S L18 (S) ANTAGON?
L21 16913 S MYELOMA
L22 5 S L20 AND L21
L23 123 S (DICKKOPF () 1) OR (DKK () 1)
L24 155 S DICKKOPF-1 OR DKK1
L25 170 S L23 OR L24
L26 61795 S OSTEO?
L27 32 S L26 AND L25

L28 7 S L27 AND L21

FILE 'PCTFULL' ENTERED AT 13:10:21 ON 25 JUL 2005
L29 1307 S WNT
L30 161 S L29 (S) ANTAG?
L31 46 S (DICKKOPF () 1) OR (DKK () 1)
L32 62 S DICKKOPF-1 OR DKK1 OR DKK-1
L33 62 S L32 OR L31
L34 27031 S OSTEO?
L35 59451 S L34 OR BONE
L36 87552 S CANCER? OR TUMOR? OR NEOPLAS?
L37 14570 S MYELOMA
L38 39 S L33 AND L34
L39 18 S L38 AND L37
L40 8 S L39 NOT PY>2002
L41 10 S L33/CLM
L42 1 S L41 AND L40
L43 4 S L33/AB
L44 1 S L42 AND L35
L45 0 S D IBIB

FILE 'DISSABS' ENTERED AT 13:16:14 ON 25 JUL 2005
L46 4 S DICKKOPF-1 OR DKK1 OR DKK-1
L47 3245 S OSTEO?
L48 0 S L47 AND L46
L49 0 S L46 AND MYELOMA

L50 FILE 'PCTFULL' ENTERED AT 13:17:23 ON 25 JUL 2005
4 S L43 AND L35

\Rightarrow

---Logging off of STN---

=> .
Executing the logoff script...

=> LOG Y

COST IN U.S. DOLLARS	SINCE FILE ENTRY	TOTAL SESSION
FULL ESTIMATED COST	5.34	68.46

STN INTERNATIONAL LOGOFF AT 13:18:35 ON 25 JUL 2005

Connecting via Winsock to STN

Welcome to STN International! Enter x:x

LOGINTID: SSSPTA1642BJF

PASSWORD:

TERMINAL (ENTER 1, 2, 3, OR ?):2

* * * * * * * * * * * * * Welcome to STN International * * * * * * * * * * * *

NEWS 1 Web Page URLs for STN Seminar Schedule - N. America
NEWS 2 "Ask CAS" for self-help around the clock
NEWS 3 FEB 28 PATDPAFULL - New display fields provide for legal status data from INPADOC
NEWS 4 FEB 28 BABS - Current-awareness alerts (SDIs) available
NEWS 5 MAR 02 GBFULL: New full-text patent database on STN
NEWS 6 MAR 03 REGISTRY/ZREGISTRY - Sequence annotations enhanced
NEWS 7 MAR 03 MEDLINE file segment of TOXCENTER reloaded
NEWS 8 MAR 22 KOREPAT now updated monthly; patent information enhanced
NEWS 9 MAR 22 Original IDE display format returns to REGISTRY/ZREGISTRY
NEWS 10 MAR 22 PATDPASPC - New patent database available
NEWS 11 MAR 22 REGISTRY/ZREGISTRY enhanced with experimental property tags
NEWS 12 APR 04 EPFULL enhanced with additional patent information and new fields
NEWS 13 APR 04 EMBASE - Database reloaded and enhanced
NEWS 14 APR 18 New CAS Information Use Policies available online
NEWS 15 APR 25 Patent searching, including current-awareness alerts (SDIs), based on application date in CA/CAplus and USPATFULL/USPAT2 may be affected by a change in filing date for U.S. applications.
NEWS 16 APR 28 Improved searching of U.S. Patent Classifications for U.S. patent records in CA/CAplus
NEWS 17 MAY 23 GBFULL enhanced with patent drawing images
NEWS 18 MAY 23 REGISTRY has been enhanced with source information from CHEMCATS
NEWS 19 JUN 06 The Analysis Edition of STN Express with Discover! (Version 8.0 for Windows) now available
NEWS 20 JUN 13 RUSSIAPAT: New full-text patent database on STN
NEWS 21 JUN 13 FRFULL enhanced with patent drawing images
NEWS 22 JUN 27 MARPAT displays enhanced with expanded G-group definitions and text labels
NEWS 23 JUL 01 MEDICONF removed from STN
NEWS 24 JUL 07 STN Patent Forums to be held in July 2005
NEWS 25 JUL 13 SCISEARCH reloaded
NEWS 26 JUL 20 Powerful new interactive analysis and visualization software, STN AnaVist, now available

NEWS EXPRESS JUNE 13 CURRENT WINDOWS VERSION IS V8.0, CURRENT MACINTOSH VERSION IS V6.0c(ENG) AND V6.0Jc(JP), AND CURRENT DISCOVER FILE IS DATED 13 JUNE 2005

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*ENCOMPAT - EnCompass Patent File 1964-present (Supporters)
*ENCOMPAT2 - EnCompass Patent File 1964-Present (Non-Supporters)

* The files listed above are temporarily unavailable.

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=> file medline  
COST IN U.S. DOLLARS  
FULL ESTIMATED COST
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| SINCE ENTRY | TOTAL SESSION |
|-------------|---------------|
| 0.21 | 0.21 |

FILE 'MEDLINE' ENTERED AT 16:16:12 ON 25 JUL 2005

FILE LAST UPDATED: 23 JUL 2005 (20050723/UP). FILE COVERS 1950 TO DATE.

On December 19, 2004, the 2005 MeSH terms were loaded.

The MEDLINE reload for 2005 is now available. For details enter HELP RLOAD at an arrow prompt (=>). See also:

<http://www.nlm.nih.gov/mesh/>
http://www.nlm.nih.gov/pubs/techbull/nd04/nd04_mesh.html

OLDMEDLINE now back to 1950.

MEDLINE thesauri in the /CN, /CT, and /MN fields incorporate the MeSH 2005 vocabulary.

This file contains CAS Registry Numbers for easy and accurate substance identification.

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=> s bone  
    424243 BONE  
    91740 BONES  
L1    446342 BONE  
          (BONE OR BONES)
```

```
=> s (dickkopf () 1) or (dickkopf-1) or dickkopf1 or (dkk1) or (dkk-1) or (dkk () 1)  
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    8 DICKKOPFS  
    90 DICKKOPF  
          (DICKKOPF OR DICKKOPFS)  
3513889 1  
    49 DICKKOPF (W) 1  
    85 DICKKOPF  
    8 DICKKOPFS  
    90 DICKKOPF  
          (DICKKOPF OR DICKKOPFS)  
3513889 1  
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          (DICKKOPF(W)1)  
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    106 DKK1  
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    9 DKKS  
    121 DKK  
          (DKK OR DKKS)  
3513889 1  
    44 DKK-1  
          (DKK(W)1)  
    119 DKK  
    9 DKKS  
    121 DKK  
          (DKK OR DKKS)  
3513889 1  
    44 DKK (W) 1  
L2    133 (DICKKOPF (W) 1) OR (DICKKOPF-1) OR DICKKOPF1 OR (DKK1) OR (DKK-  
    1) OR (DKK (W) 1)
```

```
=> s 12 and 11
```

L3 36 L2 AND L1

=> s 13 not py>2002
 1489868 PY>2002
L4 12 L3 NOT PY>2002

=> s 14 and express?
 932565 EXPRESS?
L5 9 L4 AND EXPRESS?

=> d ibib 1-4

L5 ANSWER 1 OF 9 MEDLINE on STN
ACCESSION NUMBER: 2002693855 MEDLINE
DOCUMENT NUMBER: PubMed ID: 12455632
TITLE: Bmp, Fgf and Wnt signalling in programmed cell death and chondrogenesis during vertebrate limb development: the role of Dickkopf-1.
AUTHOR: Grotewold Lars; Ruther Ulrich
CORPORATE SOURCE: Institut fur Entwicklungs- und Molekularbiologie der Tiere (EMT), Heinrich-Heine-Universitat, Dusseldorf, Germany.
SOURCE: International journal of developmental biology, (2002) 46 (7) 943-7.
PUB. COUNTRY: Journal code: 8917470. ISSN: 0214-6282.
Spain
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200306
ENTRY DATE: Entered STN: 20021214
Last Updated on STN: 20030619
Entered Medline: 20030618

L5 ANSWER 2 OF 9 MEDLINE on STN
ACCESSION NUMBER: 2002131765 MEDLINE
DOCUMENT NUMBER: PubMed ID: 11867524
TITLE: The Wnt antagonist Dickkopf-1 is regulated by Bmp signaling and c-Jun and modulates programmed cell death.
AUTHOR: Grotewold Lars; Ruther Ulrich
CORPORATE SOURCE: Entwicklungs- und Molekularbiologie der Tiere, Heinrich-Heine Universitat, D-40225 Dusseldorf, Germany.. lars.grotewold@uni-duesseldorf.de
SOURCE: EMBO journal, (2002 Mar 1) 21 (5) 966-75.
Journal code: 8208664. ISSN: 0261-4189.
PUB. COUNTRY: England: United Kingdom
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200205
ENTRY DATE: Entered STN: 20020228
Last Updated on STN: 20020515
Entered Medline: 20020514

L5 ANSWER 3 OF 9 MEDLINE on STN
ACCESSION NUMBER: 2001447406 MEDLINE
DOCUMENT NUMBER: PubMed ID: 11291860
TITLE: The role of the homeodomain protein Bozozok in zebrafish axis formation.
AUTHOR: Solnica-Krezel L; Driever W
CORPORATE SOURCE: Department of Molecular Biology, Vanderbilt University, Nashville, Tennessee 37235, USA.. lilianna.solnica-krezel@vanderbilt.edu
SOURCE: International journal of developmental biology, (2001) 45 (1) 299-310.

PUB. COUNTRY: Journal code: 8917470. ISSN: 0214-6282.
Spain
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200108
ENTRY DATE: Entered STN: 20010813
Last Updated on STN: 20010813
Entered Medline: 20010809

L5 ANSWER 4 OF 9 MEDLINE on STN
ACCESSION NUMBER: 2001447398 MEDLINE
DOCUMENT NUMBER: PubMed ID: 11291852
TITLE: Dickkopf1 and the Spemann-Mangold head organizer.
AUTHOR: Niehrs C; Kazanskaya O; Wu W; Glinka A
CORPORATE SOURCE: Division of Molecular Embryology, Deutsches
Krebsforschungszentrum, Heidelberg, Germany.
SOURCE: International journal of developmental biology, (2001) 45
(1) 237-40. Ref: 34
Journal code: 8917470. ISSN: 0214-6282.
Spain
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
General Review; (REVIEW)
(REVIEW, TUTORIAL)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200108
ENTRY DATE: Entered STN: 20010813
Last Updated on STN: 20010813
Entered Medline: 20010809

=> d ibib 5-7

L5 ANSWER 5 OF 9 MEDLINE on STN
ACCESSION NUMBER: 2001168646 MEDLINE
DOCUMENT NUMBER: PubMed ID: 11269304
TITLE: Development. The path to the heart and the road not taken.
AUTHOR: Olson E N
CORPORATE SOURCE: Department of Molecular Biology, University of Texas
Southwestern Medical Center, Dallas, TX 75390, USA..
eolson@hamon.swmed.edu
SOURCE: Science, (2001 Mar 23) 291 (5512) 2327-8.
Journal code: 0404511. ISSN: 0036-8075.
United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200104
ENTRY DATE: Entered STN: 20010417
Last Updated on STN: 20021218
Entered Medline: 20010412

L5 ANSWER 6 OF 9 MEDLINE on STN
ACCESSION NUMBER: 2001150174 MEDLINE
DOCUMENT NUMBER: PubMed ID: 11159911
TITLE: Wnt antagonism initiates cardiogenesis in Xenopus laevis.
AUTHOR: Schneider V A; Mercola M
CORPORATE SOURCE: Department of Cell Biology, Harvard Medical School, Boston,
Massachusetts 02115, USA.
CONTRACT NUMBER: RO1 HL59502 (NHLBI)
SOURCE: Genes & development, (2001 Feb 1) 15 (3) 304-15.
Journal code: 8711660. ISSN: 0890-9369.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)

LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200103
ENTRY DATE: Entered STN: 20010404
Last Updated on STN: 20010404
Entered Medline: 20010315

L5 ANSWER 7 OF 9 MEDLINE on STN
ACCESSION NUMBER: 2001069917 MEDLINE
DOCUMENT NUMBER: PubMed ID: 11044411
TITLE: The role of Xenopus dickkopf1 in prechordal plate specification and neural patterning.
AUTHOR: Kazanskaya O; Glinka A; Niehrs C
CORPORATE SOURCE: Division of Molecular Embryology, Deutsches Krebsforschungszentrum, Im Neuenheimer Feld 280, D-69120 Heidelberg, Germany.
SOURCE: Development (Cambridge, England), (2000 Nov) 127 (22) 4981-92.
PUB. COUNTRY: ENGLAND: United Kingdom
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200101
ENTRY DATE: Entered STN: 20010322
Last Updated on STN: 20010322
Entered Medline: 20010104

=> d his

(FILE 'HOME' ENTERED AT 16:15:45 ON 25 JUL 2005)

FILE 'MEDLINE' ENTERED AT 16:16:12 ON 25 JUL 2005
L1 446342 S BONE
L2 133 S (DICKKOPF () 1) OR (DICKKOPF-1) OR DICKKOPF1 OR (DKK1) OR (DK
L3 36 S L2 AND L1
L4 12 S L3 NOT PY>2002
L5 9 S L4 AND EXPRESS?

=> d ibib 8-9

L5 ANSWER 8 OF 9 MEDLINE on STN
ACCESSION NUMBER: 2000108581 MEDLINE
DOCUMENT NUMBER: PubMed ID: 10640703
TITLE: Requirement for anti-dorsalizing morphogenetic protein in organizer patterning.
AUTHOR: Dosch R; Niehrs C
CORPORATE SOURCE: Division of Molecular Embryology, Deutsches Krebsforschungszentrum, Im Neuenheimer Feld 280, D-69120, Heidelberg, Germany.
SOURCE: Mechanisms of development, (2000 Feb) 90 (2) 195-203.
PUB. COUNTRY: Ireland
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200004
ENTRY DATE: Entered STN: 20000505
Last Updated on STN: 20000505
Entered Medline: 20000427

L5 ANSWER 9 OF 9 MEDLINE on STN
ACCESSION NUMBER: 1999425169 MEDLINE
DOCUMENT NUMBER: PubMed ID: 10495270

TITLE: Dickkopf genes are co-ordinately expressed in mesodermal lineages.
AUTHOR: Monaghan A P; Kioschis P; Wu W; Zuniga A; Bock D; Poustka A; Delius H; Niehrs C
CORPORATE SOURCE: Division of Molecular Biology of the Cell I, Deutsches Krebsforschungszentrum, Im Neuenheimer Feld 280, D-69120, Heidelberg, Germany.
SOURCE: Mechanisms of development, (1999 Sep) 87 (1-2) 45-56.
Journal code: 9101218. ISSN: 0925-4773.
PUB. COUNTRY: Ireland
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
OTHER SOURCE: GENBANK-AJ243963; GENBANK-AJ243964
ENTRY MONTH: 200003
ENTRY DATE: Entered STN: 20000327
Last Updated on STN: 20000327
Entered Medline: 20000316

=> d 1-4

L5 ANSWER 1 OF 9 MEDLINE on STN
AN 2002693855 MEDLINE
DN PubMed ID: 12455632
TI Bmp, Fgf and Wnt signalling in programmed cell death and chondrogenesis during vertebrate limb development: the role of Dickkopf-1.
AU Grotewold Lars; Ruther Ulrich
CS Institut fur Entwicklungs- und Molekularbiologie der Tiere (EMT), Heinrich-Heine-Universitat, Dusseldorf, Germany.
SO International journal of developmental biology, (2002) 46 (7) 943-7.
Journal code: 8917470. ISSN: 0214-6282.
CY Spain
DT Journal; Article; (JOURNAL ARTICLE)
LA English
FS Priority Journals
EM 200306
ED Entered STN: 20021214
Last Updated on STN: 20030619
Entered Medline: 20030618

L5 ANSWER 2 OF 9 MEDLINE on STN
AN 2002131765 MEDLINE
DN PubMed ID: 11867524
TI The Wnt antagonist Dickkopf-1 is regulated by Bmp signaling and c-Jun and modulates programmed cell death.
AU Grotewold Lars; Ruther Ulrich
CS Entwicklungs- und Molekularbiologie der Tiere, Heinrich-Heine Universitat, D-40225 Dusseldorf, Germany.. lars.grotewold@uni-duesseldorf.de
SO EMBO journal, (2002 Mar 1) 21 (5) 966-75.
Journal code: 8208664. ISSN: 0261-4189.
CY England: United Kingdom
DT Journal; Article; (JOURNAL ARTICLE)
LA English
FS Priority Journals
EM 200205
ED Entered STN: 20020228
Last Updated on STN: 20020515
Entered Medline: 20020514

L5 ANSWER 3 OF 9 MEDLINE on STN
AN 2001447406 MEDLINE
DN PubMed ID: 11291860
TI The role of the homeodomain protein Bozozok in zebrafish axis formation.

AU Solnica-Krezel L; Driever W
CS Department of Molecular Biology, Vanderbilt University, Nashville,
Tennessee 37235, USA.. lilianna.solnica-krezel@vanderbilt.edu
SO International journal of developmental biology, (2001) 45 (1) 299-310.
Journal code: 8917470. ISSN: 0214-6282.
CY Spain
DT Journal; Article; (JOURNAL ARTICLE)
LA English
FS Priority Journals
EM 200108
ED Entered STN: 20010813
Last Updated on STN: 20010813
Entered Medline: 20010809

L5 ANSWER 4 OF 9 MEDLINE on STN
AN 2001447398 MEDLINE
DN PubMed ID: 11291852
TI Dickkopf1 and the Spemann-Mangold head organizer.
AU Niehrs C; Kazanskaya O; Wu W; Glinka A
CS Division of Molecular Embryology, Deutsches Krebsforschungszentrum,
Heidelberg, Germany.
SO International journal of developmental biology, (2001) 45 (1) 237-40.
Ref: 34
Journal code: 8917470. ISSN: 0214-6282.
CY Spain
DT Journal; Article; (JOURNAL ARTICLE)
General Review; (REVIEW)
(REVIEW, TUTORIAL)
LA English
FS Priority Journals
EM 200108
ED Entered STN: 20010813
Last Updated on STN: 20010813
Entered Medline: 20010809

=> d kwic 4

L5 ANSWER 4 OF 9 MEDLINE on STN
TI Dickkopf1 and the Spemann-Mangold head organizer.
AB . . . the Spemann-Mangold organizer may be mediated by secreted Wnt
antagonists. Wnts are potent posteriorizing factors and antagonize the
Spemann-Mangold organizer. Dickkopf1 (dkk1) encodes a
secreted effector expressed in head organizing centers of
Xenopus, mouse and zebrafish. It acts as a Wnt inhibitor and is able
together with. . . anteriorizes both mesendoderm and neuroectoderm,
promoting prechordal plate and forebrain fates. Injection of inhibitory
antibodies leads to microcephaly and cyclopia. Dkk1 thus is an
essential mediator of the vertebrate head organizer.
CT Animals
Body Patterning
Bone Morphogenetic Proteins: AI, antagonists & inhibitors
Embryonic Induction
Head: EM, embryology
Mice
*Organizers, Embryonic: PH, physiology
Proteins: GE, genetics
CN 0 (Bone Morphogenetic Proteins); 0 (Proteins); 0 (Proto-Oncogene
Proteins); 0 (Wnt proteins); 0 (Zebrafish Proteins); 0 (dkk1
protein, Xenopus); 0 (wnt8b protein, zebrafish)

=> d kwic 2

L5 ANSWER 2 OF 9 MEDLINE on STN
TI The Wnt antagonist Dickkopf-1 is regulated by Bmp signaling and c-Jun and modulates programmed cell death.
AB Dickkopf-1 (Dkk-1) has been shown to be a potent inhibitor of Wnt/beta-catenin signaling in a variety of assays and organisms. In this study, we show that expression of Dkk-1 overlaps significantly with the sites of programmed cell death in normal as well as mutant vertebrate limb development, and identify several of its upstream regulators, one of which is Bmp-4. Interestingly, Bmp-4 only activates Dkk-1 when it concomitantly induces apoptosis. Moreover, Dkk-1 is heavily up-regulated by UV irradiation and several other genotoxic stimuli. We further show that normal expression of Dkk-1 is dependent on the Ap-1 family member c-Jun and that overexpression of Dkk-1 enhances Bmp-triggered apoptosis in the vertebrate limb. Taken together, our results provide evidence for an important role of Dkk-1-mediated inhibition of Wnt/beta-catenin signaling in response to different stress signals that all converge on the activation of c-Jun in vivo.

CT Animals
Apoptosis: GE, genetics
Apoptosis: PH, physiology
Bone Morphogenetic Proteins: AI, antagonists & inhibitors
Bone Morphogenetic Proteins: PD, pharmacology
*Bone Morphogenetic Proteins: PH, physiology
Chick Embryo
Cytoskeletal Proteins: AI, antagonists & inhibitors
DNA-Binding Proteins: BI, biosynthesis
DNA-Binding Proteins: GE, genetics
. Implants
Enzyme Inhibitors: PD, pharmacology
*Extremities: EM, embryology
Fibroblast Growth Factors: PD, pharmacology
Fibroblasts: DE, drug effects
Fibroblasts: ME, metabolism
Gene Expression Regulation, Developmental: DE, drug effects
*Gene Expression Regulation, Developmental: PH, physiology
Gene Expression Regulation, Developmental: RE, radiation effects
Mesoderm: ME, metabolism
Mice
Mice, Knockout
Morphogenesis
Protein Biosynthesis
Proteins: GE, genetics
Proteins: . . .
CN 0 (Bone Morphogenetic Proteins); 0 (Cytoskeletal Proteins); 0 (DNA-Binding Proteins); 0 (Drug Implants); 0 (Enzyme Inhibitors); 0 (Proteins); 0 (Proto-Oncogene Proteins); 0. . . 0 (Recombinant Fusion Proteins); 0 (Trans-Activators); 0 (Transcription Factor AP-1); 0 (Transcription Factors); 0 (Wnt proteins); 0 (Zebrafish Proteins); 0 (bone morphogenetic protein 4); 0 (dkk1 protein, Xenopus); 0 (hedgehog protein, vertebrate); 0 (lymphoid enhancer-binding factor 1); 0 (wnt8b protein, zebrafish)

=> d kwic 5

L5 ANSWER 5 OF 9 MEDLINE on STN
CT Animals
*Blood Cells
Bone Morphogenetic Proteins: ME, metabolism
Ca(2+)-Calmodulin Dependent Protein Kinase: ME, metabolism
Central Nervous System: EM, embryology
Central Nervous System: ME, metabolism
Cytoskeletal Proteins: ME, metabolism

Drosophila: EM, embryology
Drosophila: ME, metabolism
*Drosophila Proteins
*Embryonic Induction
Endoderm: PH, physiology
 Gene Expression Regulation, Developmental
Glycogen Synthase Kinase 3
*Heart: EM, embryology
Hematopoiesis
Insect Proteins: ME, metabolism
Mesoderm: CY, cytology
Mesoderm: . . .
CN 0 (Bone Morphogenetic Proteins); 0 (Cytoskeletal Proteins); 0 (Drosophila Proteins); 0 (Insect Proteins); 0 (Proteins); 0 (Trans-Activators); 0 (Transcription Factors); 0 (Wnt-3 protein); 0 (Xenopus Proteins); 0 (crescent protein, Xenopus); 0 (dkk1 protein, Xenopus); 0 (dpp protein, Drosophila); 0 (wnt8a protein, Zebrafish); EC 2.7.1.123 (Ca(2+)-Calmodulin Dependent Protein Kinase); EC 2.7.1.37 (Glycogen Synthase). . .

=> s osteo?
L6 211167 OSTEOT?

=> d his

(FILE 'HOME' ENTERED AT 16:15:45 ON 25 JUL 2005)

FILE 'MEDLINE' ENTERED AT 16:16:12 ON 25 JUL 2005

L1 446342 S BONE
L2 133 S (DICKKOPF () 1) OR (DICKKOPF-1) OR DICKKOPF1 OR (DKK1) OR (DK
L3 36 S L2 AND L1
L4 12 S L3 NOT PY>2002
L5 9 S L4 AND EXPRESS?
L6 211167 S OSTEOT?

=> s 12 and 16
L7 24 L2 AND L6

=> s 15 not py>2002
 1489868 PY>2002
L8 9 L5 NOT PY>2002

=> s 18 not py>2001
 2029769 PY>2001
L9 7 L8 NOT PY>2001

=> d ibib 1-4

L9 ANSWER 1 OF 7 MEDLINE on STN
ACCESSION NUMBER: 2001447406 MEDLINE
DOCUMENT NUMBER: PubMed ID: 11291860
TITLE: The role of the homeodomain protein Bozozok in zebrafish axis formation.
AUTHOR: Solnica-Krezel L; Driever W
CORPORATE SOURCE: Department of Molecular Biology, Vanderbilt University, Nashville, Tennessee 37235, USA.. lilianna.solnica-krezel@vanderbilt.edu
SOURCE: International journal of developmental biology, (2001) 45 (1) 299-310.
 Journal code: 8917470. ISSN: 0214-6282.
PUB. COUNTRY: Spain
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals

ENTRY MONTH: 200108
ENTRY DATE: Entered STN: 20010813
Last Updated on STN: 20010813
Entered Medline: 20010809

L9 ANSWER 2 OF 7 MEDLINE on STN
ACCESSION NUMBER: 2001447398 MEDLINE
DOCUMENT NUMBER: PubMed ID: 11291852
TITLE: Dickkopf1 and the Spemann-Mangold head organizer.
AUTHOR: Niehrs C; Kazanskaya O; Wu W; Glinka A
CORPORATE SOURCE: Division of Molecular Embryology, Deutsches
Krebsforschungszentrum, Heidelberg, Germany.
SOURCE: International journal of developmental biology, (2001) 45
(1) 237-40. Ref: 34
Journal code: 8917470. ISSN: 0214-6282.
PUB. COUNTRY: Spain
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
General Review; (REVIEW)
(REVIEW, TUTORIAL)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200108
ENTRY DATE: Entered STN: 20010813
Last Updated on STN: 20010813
Entered Medline: 20010809

L9 ANSWER 3 OF 7 MEDLINE on STN
ACCESSION NUMBER: 2001168646 MEDLINE
DOCUMENT NUMBER: PubMed ID: 11269304
TITLE: Development. The path to the heart and the road not taken.
AUTHOR: Olson E N
CORPORATE SOURCE: Department of Molecular Biology, University of Texas
Southwestern Medical Center, Dallas, TX 75390, USA..
eolson@hamon.swmed.edu
SOURCE: Science, (2001 Mar 23) 291 (5512) 2327-8.
Journal code: 0404511. ISSN: 0036-8075.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200104
ENTRY DATE: Entered STN: 20010417
Last Updated on STN: 20021218
Entered Medline: 20010412

L9 ANSWER 4 OF 7 MEDLINE on STN
ACCESSION NUMBER: 2001150174 MEDLINE
DOCUMENT NUMBER: PubMed ID: 11159911
TITLE: Wnt antagonism initiates cardiogenesis in *Xenopus laevis*.
AUTHOR: Schneider V A; Mercola M
CORPORATE SOURCE: Department of Cell Biology, Harvard Medical School, Boston,
Massachusetts 02115, USA.
CONTRACT NUMBER: R01 HL59502 (NHLBI)
SOURCE: Genes & development, (2001 Feb 1) 15 (3) 304-15.
Journal code: 8711660. ISSN: 0890-9369.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200103
ENTRY DATE: Entered STN: 20010404
Last Updated on STN: 20010404
Entered Medline: 20010315

=> d kwic 2

L9 ANSWER 2 OF 7 MEDLINE on STN
TI Dickkopf1 and the Spemann-Mangold head organizer.
AB . . . the Spemann-Mangold organizer may be mediated by secreted Wnt antagonists. Wnts are potent posteriorizing factors and antagonize the Spemann-Mangold organizer. Dickkopf1 (dkk1) encodes a secreted effector expressed in head organizing centers of Xenopus, mouse and zebrafish. It acts as a Wnt inhibitor and is able together with . . . anteriorizes both mesendoderm and neuroectoderm, promoting prechordal plate and forebrain fates. Injection of inhibitory antibodies leads to microcephaly and cyclopia. Dkk1 thus is an essential mediator of the vertebrate head organizer.

CT Animals

Body Patterning

Bone Morphogenetic Proteins: AI, antagonists & inhibitors

Embryonic Induction

Head: EM, embryology

Mice

*Organizers, Embryonic: PH, physiology

Proteins: GE, genetics

CN 0 (Bone Morphogenetic Proteins); 0 (Proteins); 0 (Proto-Oncogene Proteins); 0 (Wnt proteins); 0 (Zebrafish Proteins); 0 (dkk1 protein, Xenopus); 0 (wnt8b protein, zebrafish)

=> d his .

(FILE 'HOME' ENTERED AT 16:15:45 ON 25 JUL 2005)

FILE 'MEDLINE' ENTERED AT 16:16:12 ON 25 JUL 2005

L1 446342 S BONE
L2 133 S (DICKKOPF () 1) OR (DICKKOPF-1) OR DICKKOPF1 OR (DKK1) OR (DK
L3 36 S L2 AND L1
L4 12 S L3 NOT PY>2002
L5 9 S L4 AND EXPRESS?
L6 211167 S OSTEO?
L7 24 S L2 AND L6
L8 9 S L5 NOT PY>2002
L9 7 S L8 NOT PY>2001

=> s 17 not py>2001

2029769 PY>2001

L10 0 L7 NOT PY>2001

=> s 17 not py>2002

1489868 PY>2002

L11 3 L7 NOT PY>2002

=> d ibib 1-3

L11 ANSWER 1 OF 3 MEDLINE on STN

ACCESSION NUMBER: 2002280313 MEDLINE

DOCUMENT NUMBER: PubMed ID: 12021176

TITLE: Global gene profiling in human endometrium during the window of implantation.

AUTHOR: Kao L C; Tulac S; Lobo S; Imani B; Yang J P; Germeyer A; Osteen K; Taylor R N; Lessey B A; Giudice L C

CORPORATE SOURCE: Department of Gynecology and Obstetrics, Stanford University, Stanford, California 94305, USA.

CONTRACT NUMBER: U54 HD31398 (NICHD)

SOURCE: Endocrinology, (2002 Jun) 143 (6) 2119-38.

JOURNAL CODE: 0375040. ISSN: 0013-7227.

PUB. COUNTRY: United States

DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Abridged Index Medicus Journals; Priority Journals
ENTRY MONTH: 200206
ENTRY DATE: Entered STN: 20020522
Last Updated on STN: 20020619
Entered Medline: 20020618

L11 ANSWER 2 OF 3 MEDLINE on STN
ACCESSION NUMBER: 2002275003 MEDLINE
DOCUMENT NUMBER: PubMed ID: 12015398
TITLE: Regulation of bone formation and vision by LRP5.
COMMENT: Comment on: N Engl J Med. 2002 May 16;346(20):1513-21.
PubMed ID: 12015390
AUTHOR: Patel Millan S; Karsenty Gerard
SOURCE: New England journal of medicine, (2002 May 16) 346 (20)
1572-4.
Journal code: 0255562. ISSN: 1533-4406.
PUB. COUNTRY: United States
DOCUMENT TYPE: Commentary
Editorial
LANGUAGE: English
FILE SEGMENT: Abridged Index Medicus Journals; Priority Journals; Space
Life Sciences
ENTRY MONTH: 200205
ENTRY DATE: Entered STN: 20020517
Last Updated on STN: 20020623
Entered Medline: 20020522

L11 ANSWER 3 OF 3 MEDLINE on STN
ACCESSION NUMBER: 2002274995 MEDLINE
DOCUMENT NUMBER: PubMed ID: 12015390
TITLE: High bone density due to a mutation in LDL-receptor-related
protein 5.
COMMENT: Comment in: N Engl J Med. 2002 May 16;346(20):1572-4.
PubMed ID: 12015398
Comment in: N Engl J Med. 2002 Sep 19;347(12):943-4; author
reply 943-4. PubMed ID: 12239268
Comment in: N Engl J Med. 2002 Sep 19;347(12):943-4; author
reply 943-4. PubMed ID: 12240686
Comment in: N Engl J Med. 2004 May 13;350(20):2096-9;
author reply 2096-9. PubMed ID: 15141052
AUTHOR: Boyden Lynn M; Mao Junhao; Belsky Joseph; Mitzner Lyle;
Farhi Anita; Mitnick Mary A; Wu Dianqing; Insogna Karl;
Lifton Richard P
CORPORATE SOURCE: Department of Genetics, Yale University School of Medicine,
New Haven, Connecticut 06510, USA.
CONTRACT NUMBER: AG15345 (NIA)
AR46032 (NIAMS)
CA85420 (NCI)
RR00125 (NCRR)
SOURCE: New England journal of medicine, (2002 May 16) 346 (20)
1513-21.
Journal code: 0255562. ISSN: 1533-4406.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Abridged Index Medicus Journals; Priority Journals
ENTRY MONTH: 200205
ENTRY DATE: Entered STN: 20020517
Last Updated on STN: 20020926
Entered Medline: 20020522

=> d kwic 3

L11 ANSWER 3 OF 3 MEDLINE on STN

AB BACKGROUND: Osteoporosis is a major public health problem of largely unknown cause. Loss-of-function mutations in the gene for low-density lipoprotein receptor-related protein 5 (LRP5), which acts in the Wnt signaling pathway, have been shown to cause osteoporosis -pseudoglioma. METHODS: We performed genetic and biochemical analyses of a kindred with an autosomal dominant syndrome characterized by high bone density. . . flies to humans. Markers of bone resorption were normal in the affected subjects, whereas markers of bone formation such as osteocalcin were markedly elevated. Levels of fibronectin, a known target of signaling by Wnt, a developmental protein, were also elevated. In vitro studies showed that the normal inhibition of Wnt signaling by another protein, Dickkopf-1 (Dkk -1), was defective in the presence of LRP5V171 and that this resulted in increased signaling due to unopposed Wnt activity. CONCLUSIONS:.. . LRP5 function in high bone mass and point to Dkk as a potential target for the prevention or treatment of osteoporosis

CT . . .

GE, genetics

Case-Control Studies

Chromosomes, Human, Pair 11

Genes, Dominant

Genotype

Humans

Mandible: PA, pathology

Mandible: RA, radiography

Mutation, Missense

Osteogenesis: PH, physiology

Palate: PA, pathology

Pedigree

*Point Mutation

Proteins: PD, pharmacology

Proto-Oncogene Proteins: AI, antagonists & inhibitors

*Proto-Oncogene Proteins:.. .

CN 0 (Biological Markers); 0 (Proteins); 0 (Proto-Oncogene Proteins); 0 (Receptors, LDL); 0 (Wnt proteins); 0 (Zebrafish Proteins); 0 (dkk1 protein, Xenopus); 0 (lipoprotein receptor related protein 5); 0 (wnt8b protein, zebrafish)

=> d his

(FILE 'HOME' ENTERED AT 16:15:45 ON 25 JUL 2005)

FILE 'MEDLINE' ENTERED AT 16:16:12 ON 25 JUL 2005

L1 446342 S BONE
L2 133 S (DICKKOPF () 1) OR (DICKKOPF-1) OR DICKKOPF1 OR (DKK1) OR (DK
L3 36 S L2 AND L1
L4 12 S L3 NOT PY>2002
L5 9 S L4 AND EXPRESS?
L6 211167 S OSTEO?
L7 24 S L2 AND L6
L8 9 S L5 NOT PY>2002
L9 7 S L8 NOT PY>2001
L10 0 S L7 NOT PY>2001
L11 3 S L7 NOT PY>2002

=> s lesion

141659 LESION

302187 LESIONS

L12 391994 LESION
(LESION OR LESIONS)

```
=> s l12 and l2
L13      5 L12 AND L2

=> s l13 not py>2002
     1489868 PY>2002
L14      0 L13 NOT PY>2002

=> d his

(FILE 'HOME' ENTERED AT 16:15:45 ON 25 JUL 2005)

FILE 'MEDLINE' ENTERED AT 16:16:12 ON 25 JUL 2005
L1      446342 S BONE
L2      133 S (DICKKOPF () 1) OR (DICKKOPF-1) OR DICKKOPF1 OR (DKK1) OR (DK
L3      36 S L2 AND L1
L4      12 S L3 NOT PY>2002
L5      9 S L4 AND EXPRESS?
L6      211167 S OSTEO?
L7      24 S L2 AND L6
L8      9 S L5 NOT PY>2002
L9      7 S L8 NOT PY>2001
L10     0 S L7 NOT PY>2001
L11     3 S L7 NOT PY>2002
L12     391994 S LESION
L13     5 S L12 AND L2
L14     0 S L13 NOT PY>2002
```

=>

---Logging off of STN---

=>
Executing the logoff script...

=> LOG Y

| COST IN U.S. DOLLARS | SINCE FILE ENTRY | TOTAL SESSION |
|----------------------|------------------|---------------|
| FULL ESTIMATED COST | 10.06 | 10.27 |

STN INTERNATIONAL LOGOFF AT 16:26:32 ON 25 JUL 2005